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533 Rec'd PCT/PTO 18 AUG 2000

FORM PTO-1390 (Modified) (REV 5-93) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE		ATTORNEY'S DOCKET NUMBER
TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371		40283/183
		U.S. APPLICATION NO. (If known, see 37 C F R 1.5) unassigned
INTERNATIONAL APPLICATION NO. PCT/GB99/00464	INTERNATIONAL FILING DATE February 15, 1999	PRIORITY DATE CLAIMED 19 February 1998

TITLE OF INVENTION
HISTAMINE H3 R4ECEPTOR LIGANDS

APPLICANT(S) FOR DO/EO/US
APPLICANT KALINDJIAN, Sarkis,Barret –GB; BUCK, Ildiko, Maria-GB; LINNEY, Ian, Duncan-GB; WATT, Gillian, Fairfull-GB;HARPER, Elaine, Anne-GB; SHANKLEY, Nigel, Paul-GB.

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a FIRST submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a SECOND or SUBSEQUENT submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1).
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371(c)(2))
   - ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   - ☒ has been transmitted by the International Bureau.
   - ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371(c)(3))
   - ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   - ☐ have been transmitted by the International Bureau.
   - ☐ have not been made; however, the time limit for making such amendments has NOT expired.
   - ☒ have not been made and will not be made.
8. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S.C. 371(c)(3)).
9. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371(c)(4)).
10. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371(c)(5)).

Items 11. to 16. below concern other document(s) or information included:

11. ☐ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
12. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
13. ☒ A FIRST preliminary amendment.
    ☐ A SECOND or SUBSEQUENT preliminary amendment.
14. ☐ A substitute specification.
15. ☐ A change of power of attorney and/or address letter.
16. ☐ Other items or information:

U.S. APPLICATION NO. (If known, see 37 C.F.R. 1.50	INTERNATIONAL APPLICATION NO.	ATTORNEY'S DOCKET NUMBER
unassigned	PCT/GB99/000464	040283/0183

17. ☒ The following fees are submitted:	CALCULATIONS	PTO USE ONLY
Basic National Fee (37 CFR 1.492(a)(1)-(5)): Search Report has been prepared by the EPO or JPO $840.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) $670.00		
No international preliminary examination fee paid to USPTO (37 CFR 1.482) but international search fee paid to USPTO (37 CFR 1.445(a)(2) $690.00		
Neither international preliminary examination fee (37 CFR 1.482) nor International search fee (37 CFR 1.445(a)(2)) paid to USPTO $970.00		
International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(2)-(4) $96.00		
ENTER APPROPRIATE BASIC FEE AMOUNT =	$840.00	
Surcharge of $130.00 for furnishing the oath or declaration later than 20 Months from the earliest claimed priority date (37 CFR 1.492(e))		

Claims	Number Filed		Included in Basic Fee		Extra Claims		Rate		
Total Claims	28	-	20	=	8	×	$18.00	$144.00	
Independent Claims	6	-	3	=	3	×	$78.00	$234.00	
Multiple dependent claim(s) (if applicable)							$260.0		
TOTAL OF ABOVE CALCULATIONS =								$1218.00	
Reduction by ½ for filing by small entity, if applicable. Verified Small Entity statement must also be filed. (Note 37 CFR 1.9, 1.27, 1.28).								$0.0	
SUBTOTAL =									
Processing fee of $130.00 for furnishing English translation later the 20 months from the earliest claimed priority date (37 CFR 1.492(f). +									
TOTAL NATIONAL FEE =									
Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31). $40.00 per property +									
TOTAL FEES ENCLOSED =								$1218.00	
							Amount to be: refunded	$	
							charged	$	

a. ☒ A check in the amount of $1218.00 to cover the above fees is enclosed.

b. ☐ Please charge my Deposit Account No. 19-0741 in the amount of $1460.00 to the above fees. A duplicate copy of this sheet is enclosed.

c. ☒ The Commissioner is hereby authorized to charge any additional fees which may be required, or credit any overpayment to Deposit Account No. 19-0741. A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

SEND ALL CORRESPONDENCE TO:

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Richard C Peet
SIGNATURE 35,792

NAME BERNHARD D. SAXE

REGISTRATION NUMBER 28,665

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re patent application of
Sarkis Barret KALINDJIAN *et al.*
Serial No. Unassigned
Prior Appl. No.: PCT/GB99/00464 filed 1/15/1999

For: HISTAMINE H_3 RECEPTOR LIGANDS

PRELIMINARY AMENDMENT

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Applicants respectfully request that the above-identified prior application be amended as follows:

IN THE CLAIMS:

2. (Amended) [A] The compound [according to] of claim 1, wherein R^2 is selected from the group consisting of alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C_1 to C_4 alkyl, C_1 to C_4 alkoxy or halo.

3. (Amended) [A] The compound [according to] of claim 1, wherein R^2 is selected from the group consisting of phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, tolyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

4. (Amended) [A] The compound [according to any of claims 1 to 3] of claim 1, wherein x is 0.

5. (Amended) [A] The compound [according to any of claims 1 to 3] of claim 1, wherein x is 1 or 2, and R^1 is selected from the group consisting of hydroxy, C_1 to C_9 alkoxy (optionally substituted by halo), C_1 to C_9 cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C_1 to C_4 alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C_1 to C_4 alkyl, C_1 to C_3 alkoxy or halo, and the alkoxy group is optionally substituted by halo) and C_1 to C_9 alkylamino wherein the alkyl group is optionally substituted by halo.

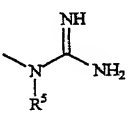
6. (Amended) [A] The compound [according to any preceding claim] of claim 1, wherein R^3 is H, C_1 to C_7 alkyl or benzyl.

7. (Amended) [A] The compound [according to any preceding claim] of claim 1, wherein R^5, R^6 and R^7 are independently selected from the group consisting of H, aryl(C_1 to C_3)alkyl and cycloalkyl(C_1 to C_3)alkyl, and are optionally substituted by halo.

8. (Amended) [A] The compound [according to any preceding claim] of claim 1, wherein Y is propylene, butylene, pentylene, hexylene, heptylene, octylene or nonylene.

9. (Amended) [A] The compound [according to any preceding claim] of claim 1, wherein $m+n \geq 3$.

10. (Amended) [A] The compound [according to] of claim 8, wherein $m+n \geq 3$, Z-R^2 is



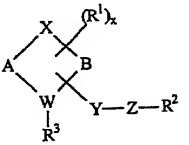
and R^5 is benzyl or halobenzyl.

Please cancel claim 11 without prejudice.

12. (Amended) A compound which is degraded *in vivo* to yield [a] the compound [according to any] of [claims] claim 1 [to 10].

13. (Amended) A pharmaceutical composition comprising a therapeutically effective amount of [a] the compound [according to any] of [claims] claim 1 [to 10], and a physiologically acceptable diluent or carrier.

28. (Amended) [The use of an H_3 receptor ligand in the manufacture of a medicament for] A method of modifying H_3 receptor activity in a patient, which comprises administering to a patient in need of a modification a therapeutically effective amount of H_3 receptor ligand or a pharmaceutically acceptable salt thereof, said H_3 receptor ligand being a compound of the formula



wherein

A is $(CH_2)_m$, m being from 1 to 3;

B is $(CH_2)_n$, n being from 1 to 3;

x is from 0 to 2;

R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

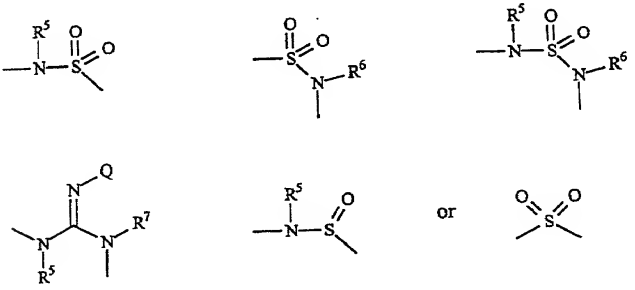
R^3 is absent when -Y-Z-R^2 is attached to W, or is H or C_1 to C_7 hydrocarbyl when -Y-Z-R^2 is not attached to W;

W is nitrogen;

X is $-CH_2-$, -O- or $-NR^4-$, R^4 being H or C_1 to C_3 alkyl;

Y replaces a hydrogen atom on any of A, B, W and X, and is C_2 to C_{10} alkylene, in which one non-terminal carbon atom may be replaced by O; and

Z is



wherein R^5, R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by 0 or N, and up to 3 hydrogen atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R^5 or R^7 to form a five-membered ring or Q is linked to R^2 to form a six-membered ring.

REMARKS

The Examiner is respectfully requested to enter the above amendments prior to examination of the instant application. The amendments are solely for the purpose of conforming the claims to standard United States claim format and do not change the scope of the invention.

Respectfully submitted,

Date August 18, 2000

By Richard Peet 35,792

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HISTAMINE H_3 RECEPTOR LIGANDS

This invention relates to compounds which bind to histamine H_3 receptors, and to methods of making such compounds.

Histamine is well known as a mediator in certain hypersensitive reactions of the body, such as allergic rashes, hayfever and asthma. These conditions are now commonly treated with potent antagonists of histamine, so-called "antihistamines".

In the 1940s, it was noted that some physiological effects of histamine, such as increased gastric acid secretion and cardiac stimulation, were not blocked by the antihistamines which were then available. This led to the proposal that histamine receptors exist in at least two distinct types, referred to as H_1 and H_2 receptors. Subsequently, H_2 antagonists (such as cimetidine, ranitidine and famotidine) were identified, and they have become important in the treatment of gastric ulcers.

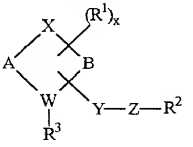
In the early 1980s, it was established that histamine also has a role as a neurotransmitter in the central nervous system. Arrang *et al.*, Nature 302, 832 to 837 (1983), proposed the existence of a third histamine receptor subtype (H_3) located presynaptically on histaminergic nerve endings. Arrang *et al.* postulated that the H_3 receptor is involved in inhibiting the synthesis and release of histamine in a negative feedback mechanism. The existence of the H_3 receptor was subsequently confirmed by the development of selective H_3 agonists and antagonists (Arrang *et al.*, Nature 327, 117 to 123 (1987)). The H_3 receptor has subsequently been shown to regulate the release of other neurotransmitters both in the central nervous system and in peripheral organs, in particular in the lungs and GI tract. In addition, H_3 receptors are reported to regulate the release of histamine from mast cells and enterochromaffin-like cells.

A need exists for potent and selective H_3 ligands (both agonists and antagonists) as tools in the study of the role of histamine as a neurotransmitter, and in its roles as a neuro-, endo- and paracrine hormone. It has also been anticipated that H_3 ligands will have therapeutic utility for a number of indications including use as sedatives, sleep regulators, anticonvulsants, regulators of hypothalamo-hypophyseal secretion, antidepressants and

modulators of cerebral circulation, and in the treatment of asthma and irritable bowel syndrome.

A number of imidazole derivatives have been proposed in the patent literature as H_3 ligands. Representative are the disclosures of EP-A-0197840, EP-A-0214058, EP-A-0458661, EP-A-0494010, EP-A-0531219, WO91/17146, WO92/15567, WO93/01812, WO93/12093, WO93/12107, WO93/12108, WO93/14070, WO93/20061, WO94/17058, WO95/06037, WO95/11894, WO95/14007, US-A-4988689 and US-A-5217986.

According to the present invention, there are provided compounds of the formula



wherein

A is $(CH_2)_m$, m being from 1 to 3;

B is $(CH_2)_n$, n being from 1 to 3;

x is from 0 to 2;

R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

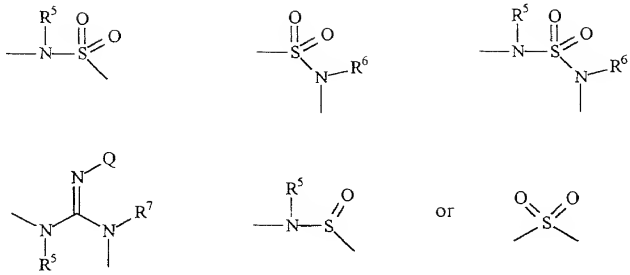
R^3 is absent when -Y-Z-R^2 is attached to W, or is H or C_1 to C_7 hydrocarbyl when -Y-Z-R^2 is not attached to W;

W is nitrogen;

X is $-CH_2-$, -O- or $-NR^4-$, R^4 being H or C_1 to C_3 alkyl;

Y replaces a hydrogen atom on any of A, B, W and X, and is C_2 to C_{10} alkylene, in which one non-terminal carbon atom may be replaced by O; and

Z is



wherein R^5, R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O or N, and up to 3 hydrogen atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R^5 or R^7 to form a five-membered ring or Q is linked to R^2 to form a six-membered ring,

and pharmaceutically acceptable salts thereof.

In preferred compounds according to the invention, x is 0 or 1, and more preferably 0. R^1, when present, is preferably selected from hydroxy, C_1 to C_9 alkoxy (optionally substituted by halo), C_1 to C_9 cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C_1 to C_4 alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C_1 to C_4 alkyl, C_1 to C_3 alkoxy or halo, and the alkoxy group is optionally substituted by halo) and C_1 to C_9 alkylamino wherein the alkyl group is optionally substituted by halo.

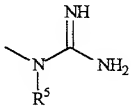
R^2 is preferably selected from alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C_1 to C_4 alkyl, C_1 to C_4 alkoxy or halo. Particularly preferred groups for R^2 include phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, tolyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

When -Y-Z-R^2 is not attached to W, R^3 is preferably C_1 to C_7 alkyl or benzyl.

In one group of compounds according to the invention, R^5, R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which one hydrogen atom may be replaced by halogen. R^5, R^6 and R^7 are preferably H, aryl(C_1 to C_3)alkyl or cycloalkyl(C_1 to C_3)alkyl, and are optionally substituted by halo.

Y is preferably C_2 to C_{10} alkylene, and more preferably propylene, butylene, pentylene , hexylene, heptylene, octylene or nonylene.

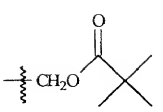
Particularly preferred compounds according to the present invention are those in which Y is propylene, butylene, pentylene , hexylene, heptylene, octylene or nonylene, $m+n \geq 3$, $Z\text{-}R^2$ is



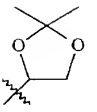
and R^5 is benzyl or halobenzyl. Such compounds, of which particular examples are given in Examples 68 to 74 below, have been found to have unusually low activity at sigma$_1$ binding sites, in addition to high affinity at H_3 receptors.

The invention also comprehends derivative compounds ("pro-drugs") which are degraded *in vivo* to yield the species of formula (I). Pro-drugs are usually (but not always) of lower potency at the target receptor than the species to which they are degraded. Pro-drugs are particularly useful when the desired species has chemical or physical properties which make its administration difficult or inefficient. For example, the desired species may be only poorly soluble, it may be poorly transported across the mucosal epithelium, or it may have an undesirably short plasma half-life. Further discussion of pro-drugs may be found in Stella, V. J. *et al.*, "Prodrugs", Drug Delivery Systems, pp. 112-176 (1985), and Drugs, 29, pp.455-473 (1985).

Pro-drug forms of the pharmacologically-active compounds of the invention will generally be compounds according to formula (I) having an acid group which is esterified or amidated. Included in such esterified acid groups are groups of the form $-COOR^8$, wherein R^8 is C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, substituted benzyl, or one of the following:



or



Amidated acid groups include groups of the formula $-CONR^9R^{10}$, wherein R^9 is H, C_1 to C_5 alkyl, phenyl, substituted phenyl, benzyl, or substituted benzyl, and R^{10} is -OH or one of the groups just recited for R^9.

Compounds of formula (I) having an amino group may be derivatised with a ketone or an aldehyde such as formaldehyde to form a Mannich base. This will hydrolyse with first order kinetics in aqueous solution.

Pharmaceutically acceptable salts of the acidic compounds of the invention include salts with inorganic cations such as sodium, potassium, calcium, magnesium, and zinc, and salts with organic bases. Suitable organic bases include N-methyl-D-glucamine, benzathine, diolamine, olamine, procaine and tromethamine.

Pharmaceutically acceptable salts of the basic compounds of the invention include salts derived from organic or inorganic acids. Suitable anions include acetate, adipate, besylate, bromide, camsylate, chloride, citrate, edisylate, estolate, fumarate, gluceptate, gluconate, glucuronate, hippurate, hyclate, hydrobromide, hydrochloride, iodide, isethionate, lactate, lactobionate, maleate, mesylate, methylbromide, methylsulfate, napsylate, nitrate, oleate, pamoate, phosphate, polygalacturonate, stearate, succinate, sulfate, sulfosalicylate, tannate, tartrate, terephthalate, tosylate and triethiodide.

The compounds of the invention may exist in various enantiomeric, diastereomeric and tautomeric forms. It will be understood that the invention comprehends the different enantiomers, diastereomers and tautomers in isolation from each other, as well as mixtures of enantiomers, diastereomers and tautomers.

The term "hydrocarbyl", as used herein, refers to monovalent groups consisting of carbon and hydrogen. Hydrocarbyl groups thus include alkyl, alkenyl, and alkynyl groups (in both straight and branched chain forms), cycloalkyl (including polycycloalkyl), cycloalkenyl, and aryl groups, and combinations of the foregoing, such as alkylaryl,

alkenylaryl, alkynylaryl, cycloalkylaryl, and cycloalkenylaryl groups. The term "hydrocarbylene" refers to corresponding divalent groups, the two free valencies being on separate atoms.

When reference is made herein to a carbon atom of a hydrocarbyl group being replaced by O, S or N, it will be understood that what is meant is that a $-CH_2-$ group is replaced by –O– or –S–, or that a  group is replaced by a group.

A "carbocyclic" group, as the term is used herein, comprises one or more closed chains or rings, which consist entirely of carbon atoms, and which may be substituted. Included in such groups are alicyclic groups (such as cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and adamantyl), groups containing both alkyl and cycloalkyl moieties (such as adamantanemethyl), and aromatic groups (such as phenyl, naphthyl, indanyl, fluorenyl, (1,2,3,4)-tetrahydronaphthyl, indenyl and isoindenyl).

The term "aryl" is used herein to refer to aromatic carbocyclic groups, including those mentioned above, which may be substituted.

A "heterocyclic" group comprises one or more closed chains or rings which have at least one atom other than carbon in the closed chain or ring, and which may be substituted. Examples include benzimidazolyl, thienyl, furanyl, pyrrolyl, imidazolyl, pyrazolyl, thiazolyl, isothiazolyl, oxazolyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrazolidinyl, tetrahydrofuranyl, pyranyl, pyronyl, pyridyl, pyrazinyl, pyridazinyl, piperidyl, piperazinyl, morpholinyl, thionaphthyl, benzofuranyl, isobenzofuryl, indolyl, oxyindolyl, isoindolyl, indazolyl, indolinyl, 7-azaindolyl, isoindazolyl, benzopyranyl, coumarinyl, isocoumarinyl, quinolyl, isoquinolyl, naphthridinyl, cinnolinyl, quinazolinyl, pyridopyridyl, benzoxazinyl, quinoxadinyl, chromenyl, chromanyl, isochromanyl and carbolinyl.

When reference is made herein to a substituted carbocyclic group (such as substituted phenyl) or a substituted heterocyclic group, the substituents are preferably from 1 to 3 in number and selected from C_1 to C_6 alkyl, C_1 to C_6 alkoxy, C_1 to C_6 alkylthio, carboxy, carboxy(C_1 to C_6)alkyl, formyl, C_1 to C_6 alkylcarbonyl, C_1 to C_6 alkylcarbonylalkoxy,

nitro, trihalomethyl, hydroxy, amino, C_1 to C_6 alkylamino, di(C_1 to C_6 alkyl)amino, halo, sulphamoyl and cyano.

The term "halogen", as used herein, refers to any of fluorine, chlorine, bromine and iodine.

Pharmaceutically acceptable salts of the acidic or basic compounds of the invention can of course be made by conventional procedures, such as by reacting the free base or acid with at least a stoichiometric amount of the desired salt-forming acid or base.

It is anticipated that the compounds of the invention can be administered by oral or parenteral routes, including intravenous, intramuscular, intraperitoneal, subcutaneous, rectal and topical administration, and inhalation.

For oral administration, the compounds of the invention will generally be provided in the form of tablets or capsules or as an aqueous solution or suspension.

Tablets for oral use may include the active ingredient mixed with pharmaceutically acceptable excipients such as inert diluents, disintegrating agents, binding agents, lubricating agents, sweetening agents, flavouring agents, colouring agents and preservatives. Suitable inert diluents include sodium and calcium carbonate, sodium and calcium phosphate, and lactose, while corn starch and alginic acid are suitable disintegrating agents. Binding agents may include starch and gelatin, while the lubricating agent, if present, will generally be magnesium stearate, stearic acid or talc. If desired, the tablets may be coated with a material such as glyceryl monostearate or glyceryl distearate, to delay absorption in the gastrointestinal tract.

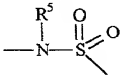
Capsules for oral use include hard gelatin capsules in which the active ingredient is mixed with a solid diluent, and soft gelatin capsules wherein the active ingredient is mixed with water or an oil such as peanut oil, liquid paraffin or olive oil.

For intramuscular, intraperitoneal, subcutaneous and intravenous use, the compounds of the invention will generally be provided in sterile aqueous solutions or suspensions, buffered to an appropriate pH and isotonicity. Suitable aqueous vehicles include Ringer's

solution and isotonic sodium chloride. Aqueous suspensions according to the invention may include suspending agents such as cellulose derivatives, sodium alginate, polyvinyl-pyrrolidone and gum tragacanth, and a wetting agent such as lecithin. Suitable preservatives for aqueous suspensions include ethyl and n-propyl p-hydroxybenzoate.

Effective doses of the compounds of the present invention may be ascertained by conventional methods. The specific dosage level required for any particular patient will depend on a number of factors, including the severity of the condition being treated, the route of administration and the weight of the patient. In general, however, it is anticipated that the daily dose (whether administered as a single dose or as divided doses) will be in the range 0.001 to 5000 mg per day, more usually from 1 to 1000 mg per day, and most usually from 10 to 200 mg per day. Expressed as dosage per unit body weight, a typical dose will be expected to be between 0.01 μg/kg and 50 mg/kg, especially between 10 μg/kg and 10 mg/kg, eg. between 100 μg/kg and 2 mg/kg.

Compounds according to the invention wherein Z is

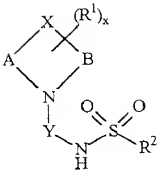


may be made by the reaction scheme which is illustrated in Figure 1.

In Figure 1, the amine (1) is reacted with a sulfonyl chloride (R^2SO_2Cl) in the presence of a base such as triethylamine, in a suitable solvent such as dichloromethane. A reaction of this type is described in greater detail below in Example 81.

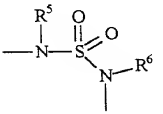
In Figure 1, and in a number of the other reaction schemes shown in the Figures, R^{3A} represents C_1 to C_7 hydrocarbyl or a suitable protecting group such as *tert*-butoxycarbonyl. If R^{3A} is a protecting group, it can be removed by conventional deprotection, and R^3 can then be introduced in the final stage by reductive amination of the secondary amine using an aldehyde of the form $R^{3B}CHO$ and sodium triacetoxyborohydride, wherein R^{3B} is a homolog of the desired R^3 group having one fewer carbon atoms in the carbon chain.

Compounds according to the invention which are of the form



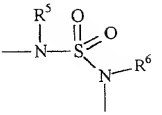
may be prepared by the reaction scheme which is depicted in Figure 2. In this scheme, the amino alcohol (2) is reacted with a sulfonyl chloride of the form R^2SO_2Cl to form compound (4). This reaction is conducted in the presence of a base such as triethylamine. A suitable solvent for the reaction is DCM. Compound (4) is then reacted with triphenylphosphine and carbon tetrachloride (preferably in a mixture with chloroform) to form the chloro derivative (5). This in turn is reacted with the cyclic imine (6) in a suitable solvent such as DCM to form the target compound (7).

Compounds wherein Z is



may be made by the scheme illustrated in Figure 3. Chlorosulfonyl isocyanate (CSI) is first reacted with *tert*-butanol in a suitable solvent such as DCM. The reaction product (8) is then reacted with the amine (1A) in the presence of a base such as triethylamine (and preferably in DCM as solvent) to form the N-protected sulfamide (9). This is then reacted with sodium hydride and R^2Br in a solvent such as DMF to form compound (10). When the group R^5 in the target compound (11) is hydrogen, compound (10) is simply deprotected using a suitable reagent such as trifluoroacetic acid (TFA). Example 107 below illustrates the preparation of N-(4-chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)sulfamide by this route. However, when the group R^5 in the target compound is other than hydrogen, compound (10) is first treated with R^5Br in the presence of a base to form compound (10A) before deprotection.

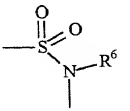
Figure 4 illustrates an alternative route for compounds wherein Z is



According to this scheme, compound (12) is reacted with the N-protected sulfamide (13) in the presence of triphenylphosphine and diethyl azodicarboxylate (DEAD) in a suitable solvent such as THF. The resulting compound (14) is then deprotected in conventional fashion to provide the target compound (15), if the group R^6 in the target compound is hydrogen. If R^6 is not hydrogen, compound (14) is reacted with R^6Br in the presence of a base to form compound (14A) before the deprotection step. This reaction scheme is further illustrated by Example 108 below.

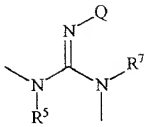
In some cases, N-substituted forms of the compound (15) may also be obtained by the reaction shown in Figure 5. In this procedure, which is exemplified in Example 135 below, the amine (1) is reacted with sulfamide (16) and an amine of the form R^2R^6NH.

Figure 6 illustrates a scheme for preparing compounds wherein Z is



In this scheme, Y^2 represents a bond or a C_1 to C_8 alkylene group. Dimethylsulfoxide is first added to oxalyl chloride (in a suitable solvent such as DCM) at reduced temperature. Compound (17), containing a free hydroxyl group, is then added, followed by a base such as triethylamine. The resulting aldehyde (18) is then reacted with the N-protected methyl sulfonamide (19) to yield compound (20). The N-protected methyl sulfonamide (19) is suitably prepared by reaction of an amine of the form R^2NH_2 with mesyl chloride, followed by *tert*-butoxycarbonyl protection. Compound (20) is then reduced (e.g. by hydrogenation in the presence of a palladium-on-charcoal catalyst) to form the target compound (21) in which R^6 is hydrogen. Example 136 below illustrates a synthesis by this route. If R^6 is to be other than hydrogen, compound (21) is reacted with R^6Br in the presence of a base to form compound (21A).

Figure 7 illustrates a scheme for preparing compounds wherein Z is

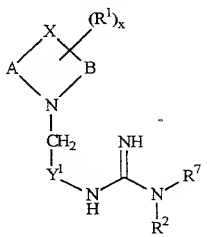


According to this scheme, the amine (1) is reacted with 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) in a suitable solvent such as THF. The resulting N-protected guanidine (23) is then deprotected using any appropriate means, such as hydrogen chloride-dioxan, to yield the target compound (24) in which R^7 is hydrogen. If R^7 in the target compound is other than hydrogen, compound (23) is reacted with R^7Br in the presence of a base to yield compound (23A) before the deprotection step. An illustrative synthesis of this type is given below in Example 1.

Figure 8 illustrates a suitable route for the preparation of guanidine derivatives wherein R^2 is other than hydrogen. According to this scheme, compound (22) is first reacted with sodium hydride (in a suitable solvent such as DMF), and then with a compound of the form R^2Br to yield the guanidine derivative (25). This is then reacted with the amine (1), and subsequently deprotected, in a manner analogous to that shown in Figure 7. A preparation of this type is illustrated in Example 2 below.

Compound (25) may alternatively be derived from compound (22) by reaction with an alcohol of the form R^2OH in the presence of triphenylphosphine and DEAD, preferably in THF as solvent. This variation is illustrated in Example 3 below.

An alternative route for the preparation of compounds of the form



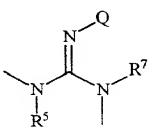
(in which Y^1 represents a C_1 to C_9 alkylene group) is illustrated in Figure 9. As shown in Figure 9, 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (22) is reacted with an enol of the form $HO\text{-}Y^1\text{-}CH{=}CH_2$ in the presence of triphenylphosphine and

DEAD The resulting compound (26) is then reacted with $R^2R^7NH_2$ to provide compound (27), which is subsequently converted to the corresponding aldehyde (28) by treatment first with ozone and then with methylsulfide. Reaction of the aldehyde with the cyclic imine (29) in the presence of triacetoxyborohydride then affords the compound (30), from which the target compound (31) may be obtained by conventional deprotection methods. A synthesis of this type is illustrated in Example 17 below.

Compounds according to the invention in which Z is a sulfinamide moiety may be prepared by the reaction scheme illustrated in Figure 10. According to this scheme, the thiol compound R^2SH (32) is reacted with N-bromosuccinimide in methanol, to provide the sulfinic acid ester (33). This is then reacted with the amine (1) and lithium diisopropylamide to provide the target compound (34). Example 87 below provides further details of this preparative method.

Compounds in which Z is a sulfone group may be prepared by the method shown in Figure 11, in which Y^1 represents a C_1 to C_9 alkylene group. In this method, sodium hydride is added to the thiol compound R^2SH (32), followed by an appropriate ester (e.g. the ethyl ester) of an acid of the form $Br\text{-}Y^1\text{-}COOH$ (35), to form the sulfanyl compound (36). This is then oxidised (e.g. with *meta*-chloroperoxybenzoic acid) to the corresponding sulfonyl compound (37). Appropriate reduction (e.g. with lithium aluminium hydride) then provides the alcohol (38), which in turn is oxidised to the aldehyde (39) using a reagent such as sulfur trioxide-pyridine. Finally, this is then reacted with the cyclic imine (6) under conditions analogous to those described above with reference to Figure 9. A synthesis of this type is illustrated in Example 88 below.

Figures 12 to 16 illustrate further routes for preparing compounds according to the invention wherein Z is



According to Figure 12, the N-protected amine (40) is alkylated with an appropriate alkene to form trisubstituted amine (40A). This is deprotected and guanylated to yield

guanidine derivative (41). Depending on the desired degree of N-substitution, guanidine derivative (41) can be treated in either of the following two ways. In one method, guanidine derivative (41) is alkylated with an appropriate alkylating agent and then oxidised by ozonolysis to yield aldehyde (42), which is reductively aminated and deprotected to yield target compound (43). Alternatively, guanidine derivative (41) is oxidised by ozonolysis without prior alkylation to yield aldehyde (44), which is similarly reductively aminated and deprotected to yield target compound (45).

A further route to target compound (45) is to reverse the order of guanylation and ozonolysis/ reductive amination. Hence trisubstituted amine (40A) is ozonolysed, reductively aminated and deprotected to form amine (40B). This is then guanylated and deprotected to yield target compound (45). This synthesis is illustrated in Example 68 below.

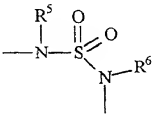
According to Figure 13, disubstituted amine (46) is guanylated to yield N-protected guanidine (47), which is alkylated with an appropriate alkylating agent, preferably a dibromide. The resulting compound (48) is aminated with an appropriate amine and deprotected to form target compound (49). Example 50 illustrates this synthesis.

According to Figure 14, the acid chloride (50) is acylated with an appropriate aminoalcohol. The hydroxy group of the resulting amide (51) is tosylated and then substituted by amination with an appropriate amine to yield amide (52). The carbonyl group of the amide (52) is then fully reduced to form amine (53), which is guanylated and deprotected to yield target compound (54). This synthesis is illustrated by Example 77.

According to Figure 15, the N-protected amine (40) is alkylated with an appropriate alkylating agent to yield substituted amine (55), in which L represents a leaving group such as bromine. This is reacted with the appropriate cyclic amine to yield compound (56), which is then deprotected and guanylated to form protected target compound (57). Finally, compound (57) is fully deprotected to yield target compound (58). Example 69 below provides an illustration of this synthesis.

According to Figure 16, an appropriate amine is reacted with isothiocyanate (59) to yield thiourea (60), which is then S-alkylated by the addition of iodomethane. The resulting thiourea derivative (61) is substituted by an appropriate amine to yield target compound (62). This synthesis is illustrated by Example 19.

Figure 17 illustrates an alternative route for compounds wherein Z is



According to this scheme, N-protected sulfamide (13) is alkylated with an appropriate alcohol (63), yielding a mixture of mono- and dialkylated sulfamides (64A/B). These are then ozonolysed to form aldehydes (65A/B), which are reductively aminated to yield target compounds (66A/B). It will be understood that the desired sulfamide (64A or 64B) may be separated from the mixture (64A/B) before ozonolysis, or a mixture of aldehydes (65A/B) may be formed, with subsequent purification of the desired species. Examples 139-141 below provide further details of this preparative method.

EXPERIMENTAL

^{1}H NMR were recorded on a Bruker DRX-300 at 300MHz, the chemical shifts were recorded relative to an internal standard and all coupling constants where given are are reported in hertz as the final number following multiplicity information. All spectra were obtained in deuterochloroform unless otherwise noted. Flash column chromatography was performed on Merck silica gel 60 using the reported solvent systems. Tetrahydrofuran (THF) was dried over sodium benzophenone ketyl under argon and distilled prior to use. Dichloromethane (DCM) was dried over calcium hydride and distilled prior to use. Commercially available anhydrous N,N-dimethylformamide (DMF) was used without further purification. Commercially available hydrogen chloride in 1,4-dioxan (4M) was used to prepare hydrochloride salts as described. All reactions were carried out under a positive pressure of dry argon. All microanalyses are quoted as percentages.

Example 1

N-(3-Pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

Step a *N,N'-Bis(*tert*-butoxycarbonyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* A solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (580mg, 2.00mmol) and 3-pyrrolidin-1-yl-propylamine (665mg, 5.19mmol) in THF (20ml) and water (2ml) was heated at reflux for 1h. The solvent was evaporated at reduced pressure and the residue partitioned between ethyl acetate (50ml) and water (50ml). The aqueous phase was discarded and the organic phase was washed with brine (50ml) and then dried over anhydrous sodium sulfate. The filtrate was evaporated and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (718mg, 97%). ^{1}H NMR 11.49 (1H, br s), 8.72 (1H, br s), 3.54-3.48 (2H, m), 2.57-2.52 (6H, m), 1.79-1.72 (6H, m), 1.51 (9H, s), 1.50 (9H, s).

Step b *N-(3-Pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.* To a solution of the product from step a (718mg, 1.94mmol) in 1,4-dioxan (5ml) was added a solution of hydrogen chloride in 1,4-dioxan (4M, 4ml, 16mmol). The resultant solution was stirred at ambient temperature for 16h to give a pink suspension. The solid was removed by filtration and dried *in vacuo* at 50°C. The solid was dissolved in aqueous hydrochloric acid (1M, 10ml) and the resultant solution was heated at reflux for 1h. The solvent was removed at reduced pressure and the residue evaporated from ethanol (10ml), chloroform (10ml) and ether (10ml) to give the title compound. ^{1}H NMR (DMSO-d_6) 11.04 (1H, br s), 8.00 (1H, t, 6), 7.54-7.12 (4H, br m), 3.53-3.39 (2H, m), 3.28-3.21 (2H, m), 3.16-3.09 (2H, m), 3.01-2.93 (2H, m), 2.00-1.86 (6H, m). Microanalysis found C 37.78 H 8.44 N 22.64. $C_8H_{20}Cl_2N_4.0.48H_2O$ requires C 38.16 H 8.39 N 22.25.

Example 2

N-(4-Chlorobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

Step a *1,3'-Bis(*tert*-butoxycarbonyl)-1-(4-chlorobenzyl)-2-methyl-2-thiopseudourea.* To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.00g, 3.45mmol) in DMF (10ml) was added sodium hydride (60% dispersion in mineral oil, 167mg, 4.18mmol) in a single portion. The resultant suspension was stirred at this temperature for 1h and then treated in a single portion with 4-chlorobenzyl bromide (780mg, 3.80mmol). The cooling bath was removed and the reaction mixture was stirred at ambient temperature for 16h. Water (50ml) was added

and the aqueous phase was extracted with ethyl acetate (50ml). The aqueous phase was discarded and the organic phase washed twice with brine (40ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (9:2 hexane:ethyl acetate) to give the title compound (987mg, 69%). ^{1}H NMR 7.30 (4H, s), 4.74 (2H, s), 2.31 (3H, s), 1.53 (9H, s), 1.42 (9H, s).

Step b *N,N'-Bis(*tert-*butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 2 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR 7.27 (4H, br s), 4.78 (2H, s), 3.16 (2H, m) 2.43-2.37 (6H, br s), 1.76 (4H, m), 1.57-1.50 (2H, m), 1.50 (9H, s), 1.43 (9H, s).

Step c *N-(4-Chlorobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride*
A solution of the product of step b (1.14g, 2.00mmol) in 1,4-dioxan (5ml) was treated with hydrogen chloride in 1,4-dioxan (15ml) and the reaction mixture stirred at ambient temperature for 16h. The solvent was evaporated at reduced pressure. The residue was evaporated from DCM (30ml) to give the title compound (700mg, 95%). ^{1}H NMR (DMSO-d_6) 10.97 (1H, br s), 8.29 (1H, br s), 8.07 (1H, t, 6), 7.69 (2H, br s), 7.40 (2H, d, 8.4), 7.30 (2H, d, 8.4), 4.37 (2H, s), 3.48-3.45 (2H, m), 3.24-3.20 (2H, m), 3.08-3.03 (2H, m), 2.94-2.91 (2H, m), 2.00-1.84 (6H, m). Microanalysis found C 48.91 H 6.95 N 14.99. $C_{15}H_{25}Cl_3N_4$ requires C 48.99 H 6.85 N 15.24.

Example 3

N-(4-Methoxybenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

Step a *1,3'-Bis(*tert-*butoxycarbonyl)-1-(4-methoxybenzyl)-2-methyl-2-thiopseudourea.* To an ice-cooled solution of 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (1.45g, 5.00mmol), 4-methoxybenzyl alcohol (759mg, 5.50mmol) and triphenylphosphine (1.97g, 5.50mmol) in THF (20ml) was added diethylazodicarboxylate (1.286ml, 5.50mmol). The coolant was removed and the reaction stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue purified by flash column chromatography (90:10 hexane:ethylacetate) to give the title compound (1.105g, 54%). ^{1}H NMR 7.30-7.27 (2H, m), 6.87-6.84 (2H, m), 4.71 (2H, s), 3.80 (3H, s), 2.27 (3H, s), 1.53 (9H, s), 1.44 (9H, s).

Step b *N,N'-Bis(*tert-*butoxycarbonyl)-N'-(4-methoxybenzyl)-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* The title compound was prepared as in Example 1 step a with the product from Example 3 step a replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea. ^{1}H NMR 10.00-9.50 (1H, br s), 7.27-7.22 (2H, m), 6.82-6.80 (2H, m), 4.73 (2H, s), 3.77 (3H, s), 3.09 (2H, br s), 2.40 (4H, br s), 2.31 (2H, br m), 1.73 (4H, s), 1.49 (9H, s), 1.42 (9H, s).

Step c *N-(4-Methoxybenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 2 step c with the product of Example 3 step b replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.00 (1H, br s), 8.25 (1H, br s), 8.11 (1H, t, 6), 7.71 (2H, br s), 7.29 (2H, d, 8.4), 6.93 (2H, d, 8.4), 4.36 (2H, s), 3.73 (3H, s), 3.55-3.26 (4H, m), 3.07 (2H, m), 2.93 (2H, s), 1.96-1.86 (6H, m). Microanalysis found C 49.30 H 8.19 N 14.17. $C_{16}H_{28}Cl_2N_4O$-1.5H_2O requires C 49.23 H 8.00 N 14.35.

Example 4

N-Naphthalen-2-yl-methyl-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 2-(bromomethyl)naphthalene replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 11.00 (1H, br s), 8.39 (1H, br s), 8.13 (1H, br s), 7.94-7.85 (4H, m), 7.75 (2H, br s), 7.53-7.46 (3H, m), 4.62 (2H, d, 6), 3.48-3.32(4H, m), 3.08-3.06 (2H, m), 2.87 (2H, s), 1.93-1.84 (6H, m). Microanalysis found C 56.89 H 7.60 N 13.95. $C_{17}H_{28}Cl_2N_4$-H_2O requires C 56.86 H 7.53 N 13.96.

Example 5

N-(4-(Trifluoromethyl)benzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 1-bromomethyl-4-trifluoromethyl-benzene replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 11.06 (1H, br s), 8.47 (1H, br s), 8.21-8.18 (1H, br m), 7.77-7.73 (4H, m), 7.57 (2H, d, 9), 4.58 (2H, d, 6), 3.49-3.44(2H, m), 3.35-3.29 (2H, m), 3.13-3.07 (2H, m), 2.94 (2H, br s), 1.96-1.88 (6H, m). Microanalysis found C 52.24 H 6.92 N 15.41. $C_{16}H_{25}Cl_2N_4F_3$ C 52.53 H 6.89 N 15.31.

Example 6

N-(4-Iodobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 4-iodobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 11.04 (1H, br s), 8.32 (1H, br s), 8.13 (1H, t, 6), 7.75-7.72 (4H, m), 7 17 (2H, d, 9), 4.41 (2H, d, 6), 3.49-3 44(2H, m), 3.31-3.29 (2H, m), 3.09-3.06 (2H, m), 2.93-2 92 (2H, br m), 1.97-1.86 (6H, m). Microanalysis found C 34.05 H 6.14 N 10.42. $C_{15}H_{25}Cl_2N_4I$-$4H_2O$ C 33.91 H 6.26 N 10.55.

Example 7 *N-(3-Bromo-4-methoxy-benzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride*

The title compound was prepared as in Example 3 with (3-bromo-4-methoxy-phenyl)-methanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 8.28 (1H, br s), 8.07 (1H, t, 6), 7.70 (2H, br s), 7.58 (1H, d, 2.1), 7.36-7.33 (1H, m), 7.12 (1H, d, 8.4), 4.37 (2H, s), 3.83 (3H, s), 3.48-3.29 (4H, m), 3.10-3.08 (2H, m), 2.96-2.93 (2H, s), 1.97-1.84 (6H, m). Microanalysis found C 43.09 H 6.33 N 12.38. $C_{16}H_{27}Cl_2N_4OBr$ requires C 43.45 H 6.15 N 12.67.

Example 8

N-Benzyl-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with benzyl bromide replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 11.10 (1H, br s), 8.36 (1H, br s), 8.16 (1H, s), 7.76 (2H, br s), 7.39-7.26 (5H, m), 4.37 (2H, d, 6), 3.47-3.27 (4H, m), 3.10-2.92 (4H, m), 1.96-1.86 (6H, m). Microanalysis found C 54.09 H 7.90 N 16.71. $C_{15}H_{26}Cl_2N_4$ requires C 54.05 H 7.86 N 16.81.

Example 9

N-(4-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 with 4-bromobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 10.92 (1H, br s), 8.26 (1H, br s), 8.03 (1H, br s), 7.68 (2H, br s), 7.56 (2H, d, 9), 7.28 (2H, d, 9), 4.40-4.42 (2H, m), 3.52-3.46 (2H, m), 3.37-3.10 (2H, m), 3.11-2.94 (4H, m), 1.93-1.86 (6H, m).

Example 10

N-(3-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 with 3-bromobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 8.32 (1H, br s), 8.08 (1H, br s), 7.72 (2H, br s), 7.55-7.47 (2H, m), 7.35-7.29 (2H, m), 4.45-4.44 (2H, m), 3.47-3.30 (4H, m), 3.13-3.08 (2H, br s), 2.96 (2H, br s), 1.94-1.87 (6H, m). Microanalysis found C 38.59 H 6.72 N 12.06. $C_{15}H_{25}BrCl_2N_4$-$3H_2O$ requires C 38.64 H 6.70 N 12.02.

Example 11

N-(2-Bromobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 2 with 2-bromobenzyl bromide replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 11.11 (1H, br s), 8.17 (2H, br s), 7.79 (2H, br s), 7.67-7.64 (1H, m), 7.43-7.25 (3H, m), 4.53-4.44 (2H, m), 3.50-3.45 (2H, m), 3.31 (2H, m), 3.17-3.11 (2H, m), 2.99-2.95 (2H, m), 1.97-1.88 (6H, m). Microanalysis found C 38.46 H 6.42 N 12.10. $C_{15}H_{25}BrCl_2N_4$-$3H_2O$ requires C 38.64 H 6.70 N 12.02.

Example 12

N-Biphenyl-4-yl-methyl-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with biphenyl-4-yl-methanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 8.33 (1H, br s), 8.1 (1H, br s), 7.75 (2H, br s), 7.69-7.65 (4H, m), 7.49-7.36 (5H, m), 4.49 (2H, m), 3.50-3.46 (2H, m), 3.32 (2H, m), 3.14-3.09 (2H, m), 2.93 (2H, s), 1.96-1.86 (6H, m). Microanalysis found C 56.80 H 7.87 N 12.88. $C_{21}H_{30}Cl_2N_4$-$2H_2O$ requires C 56.63 H 7.69 N 12.58.

Example 13

N-(1H-Benzimidazol-5-yl-methyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine tris-hydrochloride.

Step a *1H-Benzimidazole-5-carboxylic acid methyl ester hydrochloride.* Hydrogen chloride gas was bubbled through an ice-cooled suspension of 5-benzimidazole carboxylic acid (8.11g, 50.0mmol) in methanol (150ml) for 30 minutes. The resultant suspension was heated at reflux for 4h to give a dark brown solution. The solution

was allowed to cool to ambient temperature and then further cooled in an ice-bath. The resulting solid was collected by vacuum filtration and washed with ether to give the title compound (11.6g, 100%). ^{1}H NMR (DMSO-d_6) 9.59 (1H, s), 1H, d, 0.3), 8.12-8 09 (1H, m), 7.96-7.93 (1H, m), 3.91 (3H, s).

Step b *1-Trityl-1H-Benzimidazole-5-carboxylic acid methyl ester.* To a solution of the product of step a (11.6g, 50mmol) and triethylamine (21.0ml, 151mmol) in chloroform (150ml) was added portionwise trityl chloride (15.33mmol). The solution was stirred at ambient temperature for 48h. The organic solution was washed sequentially with water (100ml), 10% aqueous citric acid (100ml) and brine (100ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (4:1 DCM:ethyl acetate) to afford the title compound (10.47g, 46%).

Step c *1-Trityl-1H-benzimidazol-5-yl-methanol.* To an ice-cooled stirred suspension of the product of step b (3.61g, 7.94mmol) in THF (30ml) was added dropwise a solution of lithium aluminium hydride (1.0M in THF, 10ml, 10.0mmol). The suspension was stirred at this temperature for 1h and then was quenched with saturated aqueous ammonium chloride (100ml). The aqueous solution was extracted thrice with ethyl acetate (100ml) and the combined organic phases were washed with brine (200ml). The organic phase was dried over magnesium sulfate and the filtrate was evaporated at reduced pressure and the residue recrystallised from ethyl acetate/hexane to afford the title compound (2.68g, 79%). ^{1}H NMR 7.89 (1H, s), 7.74 (1H, d, 8.4), 7.33-7.17 (17H, m), 6.44 (1H, d, 0.9), 4.45 (2H, d, 6), 1.37 (1H, t, 6).

Step d. *N-(1H-Benzimidazol-5-yl-methyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine tris-hydrochloride.*

The title compound was prepared as in Example 3 with the product from Example 13 step c replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.01 (1H, br s), 9.59 (1H, br s), 8.55 (1H, br s), 8.21 (1H, br s), 7.88-7.80 (4H, m), 7.56 (2H, d, 9), 4.64 (2H, d, 6), 4.0-3.5 (1H, br s), 3.51-3.44 (2H, m), 3.38-3.29 (2H, m), 3.14 (2H, m), 2.97-2.92 (2H, m), 1.97-1.87 (6H, m). Microanalysis found C 41.24 H 7.40 N 18.22. $C_{16}H_{27}Cl_3N_6$-$3H_2O$ requires C 41.43 H 7.17 N 18.12.

Example 14

4-(N'-(3-Pyrrolidin-1-yl-propyl)-guanidinomethyl)-benzoic acid methyl ester bis-hydrochloride.

The title compound was prepared as in Example 2 with 4-bromomethyl-benzoic acid methyl ester replacing 4-chlorobenzyl bromide in step a. ^{1}H NMR (DMSO-d_6) 11.01 (1H, br s), 8.37 (1H, br s), 8.12 (1H, br s), 7.95 (2H, d, 9), 7 74 (2H, br s), 7.45 (2H, d, 9), 4.53 (2H, d, 6), 3.84 (3H, s), 3.48-3.46 (2H, m), 3.31 (2H, m), 3.12-3.08 (2H, m), 2.96-2.94 (2H, m), 1.96-1.85 (6H, m). Microanalysis found C 48.92 H 7.66 N 13.38. $C_{17}H_{28}Cl_2N_4O_2$-1.5H_2O requires C 48.81 H 7.47 N 13.39.

Example 15

N-(4-Chlorobenzyl)-N'-(3-morpholin-4-yl-propyl)-guanidine bis-hydrochloride.

A solution of the product from Example 2 step a (535mg, 1.29mmol) and 4-(3-aminopropyl)-morpholine (0.425ml, 2.91mmol) in THF (10ml) and water (1ml) was heated at reflux for 1h. The reaction was partitioned between ethyl acetate (40ml) and water (40ml) and the aqueous phase was discarded. The organic phase was washed with brine (50ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (120:10:1 DCM:methanol:ammonia). The residue was dissolved in chloroform (5ml) and treated with hydrogen chloride in 1,4-dioxan (5ml) and the solution stirred at ambient temperature for 18h. The solvent was removed at reduced pressure and the residue suspended in 1,4-dioxan (10ml). Filtration of the suspension afforded the title compound (120mg, 24%). ^{1}H NMR (DMSO-d_6) 11.20 (1H, s), 8.28 (1H, s), 8.05 (1H, br s), 7.70 (2H, br s), 7.43 (2H, d, 8.4), 7.34 (2H, d, 8.4), 4.42 (2H, d), 4.00-3.79 (4H, m), 3.39-3.35 (6H, m), 3.11-2.99 (2H, m), 1.98-1.91 (2H, m). Microanalysis found C 47.06 H 6.63 N 13.39 $C_{15}H_{25}Cl_3N_4O$-0.28 1,4-dioxan requires C 47.41 H 6.72 N 13.71.

Example 16

N-(4-Chlorobenzyl)-N'-(2-pyrrolidin-1-yl-ethyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 2 with 2-pyrrolidin-1-yl-ethylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 11.03 (1H, br s), 8.47 (1H, br s), 8.21 (1H, br s), 7.87 (2H, br s), 7.54-7.28 (4H, m), 4.49 (2H, d, 6), 3.68-3.30 (6H, m), 3.05-2.99 (2H, m), 2.01-1.87 (4H, m). Microanalysis found C 46.84 H 6.62 N 15.72. $C_{14}H_{23}Cl_3N_4$-0.25H_2O requires C 46.94 H 6.61 N 15.64.

Example 17

N-(4-Chlorobenzyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a *1,3'-Bis(tert-butoxycarbonyl)-1-(1-pent-4-enyl)-2-methyl-2-thiopseudourea.* The title compound was prepared as in Example 3 step a with 4-penten-1-ol replacing 4-methoxybenzyl alcohol. ^{1}H NMR 5.88-5.74 (1H, m), 5.08-4.97 (2H, m), 3.54-3.49 (2H, m), 2.39 (3H, s), 2.11-2.04 (2H, m), 1.83-1.70 (2H, m), 1.51 (9H, s), 1.49 (9H, s).

Step b *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-pent-4-enyl)-guanidine.* A solution of the product from step a (1.56g, 4.36mmol) and 4-chlorobenzylamine (1.20ml, 9.83mmol) in THF (20ml) and water (2ml) was heated at reflux for 24h. The solution was diluted with ethyl acetate (30ml) and washed sequentially with water (30ml), 10% aqueous citric acid (30ml) and brine (30ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (4:1 hexane:ethyl acetate) to give the title compound (1.464g, 74%). ^{1}H NMR 7.36-7.23 (4H, m), 5.82-5.73 (1H, m), 5.03-4.96 (2H, m), 4.40 (2H, br s), 3.68 (2H, bt, 7.2), 2.08-2.01 (2H, m), 1.68-1.54 (2H, m), 1.49 (9H, s), 1.48 (9H, s).

Step c *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(1-butan-4-al)-guanidine.* Ozone gas was bubbled through a solution of the product from step b (500mg, 1.11mmol) in methanol (10ml) at -78^{0}C for 5 minutes. The blue solution was purged of colour with nitrogen and then treated at this temperature with methylsulfide (0.81ml, 11.0mmol). The reaction mixture was allowed to warm to ambient temperature and stirred at this temperature for 2h. The solvent was evaporated at reduced pressure and the residue was purified by flash column chromatography (1:1 hexane:ethyl acetate) to give the title compound (403mg, 80%). ^{1}H NMR 9.75 (1H, s), 9.5 (1H, br s), 7.34 (2H, d, 8.4) 7.24 (2H, d, 8.4), 4.40 (2H, s), 3.70 (2H, t, 7.2), 2.48 (2H, t, 7.2), 1.93-1.83 (2H, m), 1.54 (9H, s), 1.49 (9H, s).

Step d *N,N'-Bis(tert-butoxycarbonyl)-N'-(4-chlorobenzyl)-N''-(4-pyrrolidin-1-yl-butyl)-guanidine.* To an ice cooled suspension of the product of step c (400mg, 0.88mmol) and pyrrolidine (0.080ml, 0.96mmol) in 1,2-dichloroethane (3ml) was added in a single portion sodium triacetoxyborohydride (280mg, 1.32mmol). The coolant was removed and the resultant suspension stirred at ambient temperature for 2h. The reaction was quenched with saturated aqueous sodium hydrogen carbonate (30ml) and extracted twice with ethyl acetate (20ml). The combined organic phases were dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced

pressure. The residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to give the title compound (389mg, 87%). ^{1}H NMR 9.50 (1H, br s), 7.33 (2H, d, 7.8), 7.24 (2H, d, 7.8), 4.42-4.41 (2H, m), 3.68 (2H, m), 2.51 (6H, br s), 1 78 (4H, m), 1.69-1.55 (4H, m), 1.49 (9H, s), 1.48 (9H, s).

Step e *N-(4-Chlorobenzyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 2 step c. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 8.26 (1H, br s), 8.03 (1H, br s), 7.64 (2H, m), 7.24 (2H, d, 8.4), 7.33 (2H, d, 8.4), 4.42 (2H, d, 6), 3.49-3.44 (2H, m), 3.20-3.16 (2H, m), 3.11-3.06 (2H, m), 2.95-2.91 (2H, m), 1.97-1.86 (4H, m), 1.73-1.63 (2H, m), 1.56-1.49 (2H, m). Microanalysis found C 46.89 H 7.49 N 13.53. $C_{16}H_{27}Cl_3N_4$-0.61H_2O requires C 46.78 H 7.42 N 13.64.

Example 18

N-(4-Chlorobenzyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 8.28 (1H, br s), 8.00 (1H, br s), 7.64 (2H, m), 7.42 (2H, d, 8.4), 7.33 (2H, d, 8.4), 4.42 (2H, d, 6), 3.50-3.45 (2H, m), 3.20-3.13 (2H, m), 3.06-2.93 (4H, m), 1.97-1.86 (4H, m), 1.71-1.61 (2H, m), 1.53-1.43 (2H, m), 1.35-1.28 (2H, m). Microanalysis found C 48.33 H 7.59 N 13.30. $C_{17}H_{29}Cl_3N_4$-1.57H_2O requires C 48.15 H 7.64 N 13.21.

Example 19

N-(4-Chlorophenyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine.

Step a *N-(4-Chlorophenyl)-thiourea.* To stirred aqueous ammonia (880, 20ml) was added dropwise with ice-cooling a solution of 4-chlorophenylisothiocyanate (3.39g, 20.0mmol) in 1,4-dioxan (20ml). The coolant was removed and the resultant suspension stirred at ambient temperature for 2h. The solid was removed by filtration and the filter-cake washed with water (50ml). The title compound was dried *in vacuo* (50^{0}C) for 16h and isolated as a white solid (2.90g, 78%). ^{1}H NMR (DMSO-d_6) 9.72 (1H, br s), 7.61-7.32 (6H, br m).

Step b *1-(4-Chlorophenyl)-2-methyl-2-thiopseudourea hydroiodide.* To a solution of the product of step a (2.82g, 15.11mmol) in acetone (30ml) was added iodomethane (1.41ml, 22.65mmol) and the resultant reaction mixture was heated at reflux for 1h. The solvent was removed at reduced pressure and the residue suspended in ethyl

acetate (50ml). The solid was removed by filtration and the filter-cake washed with ethyl acetate (50ml) to give the title compound as a white solid (4.53g, 91%). ^{1}H NMR (DMSO-d_6) 11-9 (3H, br s), 7.57 (2H, d, 8.7), 7.36 (2H, d, 8.7), 2.68 (3H, s).

Step c *N-(4-Chlorophenyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine.* A solution of the product of step b (986mg, 3 00mmol) and N-(3-aminopropyl)-pyrrolidine (0.948ml, 7.50mmol) in ethanol (10ml) was heated at reflux for 16h. The solvent was removed at reduced pressure and the residue suspended in aqueous ammonia (880, 25ml). The solid was removed by filtration and the filter-cake washed sequentially with water (50ml) and diethyl ether (50ml) to give the title compound as a white solid (585mg, 69%). ^{1}H NMR (DMSO-d_6) 7.18-7.12 (2H, m), 6.76-6.66 (2H, m), 5.8-4.8 (3H, br s), 3.12 (2H, t, 6.9), 2.43-2.36 (6H, m), 1.69-1.56 (6H, m). Microanalysis found C 60.01 H 7.62 N 19.74. $C_{14}H_{21}ClN_4$ requires C 59.88 H 7.54 N 19.95.

Example 20

N-(2-(4-Chlorophenyl)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 2-(4-chlorophenyl)-ethanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.04 (1H, br s), 7.92 (1H, br s), 7.80 (1H, br s), 7.59 (2H, br s), 7.38-7.30 (4H, m), 3.50-3.23 (6H, m), 3.11-3.08 (2H, m), 2.98-2.92 (2H, m), 2.79 (2H, t, 7.5), 2.00-1.82 (6H, m). Microanalysis found C 50.31 H 7.17 N 14.41. $C_{16}H_{27}Cl_3N_4$ requires C 50.34 H 7.13 N 14.68.

Example 21

N-(3-(4-Chlorophenyl)propyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 3-(4-chlorophenyl)-propanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 7.92 (2H, br s), 7.58 (2H, m), 7.32 (2H, d, 9), 7.24 (2H, d, 9), 3.49-3.47 (2H, m), 3.25 (2H, m), 3.17-3.12 (4H, m), 2.99-2.77 (2H, br m), 2.63 (2H, t, 7.5), 1.97-1.71 (8H, m). Microanalysis found C 51.28 H 7.43 N 13.84. $C_{17}H_{29}Cl_3N_4$ requires C 51.59 H 7.39 N 14.16.

Example 22

N-(4-Phenylbutyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 4-phenyl-butan-1-ol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.07 (1H, br s), 7.92 (1H, br s), 7.84 (1H, br s), 7.57 (2H, br s), 7.29-7.13 (5H, m), 3.51-3.46 (2H, m), 3.28-3.26 (2H, m), 3.17-3.11 (4H, m), 2.98-2.96 (2H, m), 2.61-2.56 (2H, m), 1.97-1.84 (6H, m), 1.65-1.42 (4H, m). Microanalysis found C 52.70 H 8.77 N 13.43. $C_{17}H_{32}Cl_2N_4$-$2H_2O$ requires C 52.55 H 8.82 N 13.62.

Example 23

N-(2-(4-Chlorophenyl)ethyl)-N'-(2-pyrrolidin-1-yl-ethyl)-guanidine bis-hydrochloride.

The title compound was prepared as in example 3 with 2-(4-chlorophenyl)-ethanol replacing 4-methoxybenzyl alcohol in step a, and 2-pyrrolidin-1-yl-ethylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.97 (1H, br s), 7.94 (1H, br s), 7.86 (1H, br s), 7.68 (2H, br s), 7.38-7.31 (4H, m), 3.59-3.22 (8H, m), 3.00-2.99 (2H, m), 2.81 (2H, t, 6), 1.99-1.87 (4H, m).

Example 24

N-(2-(4-Chlorophenyl)ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 2-(4-chlorophenyl)-ethylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 7.81 (1H, br s), 7.69 (1H, br s), 7.51 (2H, m), 7.37 (2H, d, 8.7), 7.29 (2H, d, 8.7), 3.48-3.35 (4H, m), 3.14-3.06 (4H, m), 2.97-2.93 (2H, m), 2.78 (2H, t, 7.2), 2.00-1.87 (4H, m), 1.73-1.63 (2H, m), 1.53-1.43 (2H, m). Microanalysis found C 45.33 H 7.78 N 12.39. $C_{17}H_{29}Cl_3N_4$-$3H_2O$ requires C 45.39 H 7.84 N 12.45.

Example 25

N-(2-(4-Chlorophenyl)ethyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and 2-(4-chlorophenyl)-ethylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.84 (1H, br s), 7.78 (1H, br s), 7.69 (1H, br s), 7.49 (2H, br s), 7.38-7.29 (4H, m), 3.51-3.37 (4H, m), 3.14-3.03 (4H, m), 2.98-2.90 (2H, m), 2.78 (2H, t, 7.2), 1.99-1.84 (4H, m), 1.72-1.62 (2H, m), 1.48-

1.41 (2H, m), 1.36-1.29 (2H, m). Microanalysis found C 52.33 H 7.91 N 13.38. $C_{18}H_{31}Cl_3N_4$-requires C 52.75 H 7.62 N 13.67.

Example 26

N-(2-(4-Bromophenyl)ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with 2-(4-bromophenyl)-ethanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.12 (1H, br s), 8.00 (1H, br s), 7.89 (1H, br s), 7.64 (2H, br s), 7.47 (2H, d, 9), 7.25 (2H, d, 9), 3.48-3.26 (6H, m), 3.15-3.10 (2H, m), 2.99-2.95 (2H, m), 2.77 (2H, t, 7.2), 1.97-1.87 (6H, m). Microanalysis found C 44.77 H 6.59 N 13.29. $C_{16}H_{27}BrCl_2N_4$ requires C 45.09 H 6.39 N 13.14.

Example 27

N-(4-Chlorobenzyl)-N'-(2-(1-methyl-pyrrolidin-2-yl)-ethyl)-guanidine bis-hydrochloride. The product was prepared as in Example 2 with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 3-pyrrolidin-1-yl-propylamine in step a. ^{1}H NMR (DMSO-d_6) 10.84 (1H, br s), 8.28 (1H, br s), 8.05 (1H, br t, 6), 7.69 (2H, br s), 7.46-7.23 (4H, m), 4.42 (2H, d, 6), 3.46-2.90 (5H, m), 2.74-2.73 (3H, br s), 2.14-1.87 (6H, m). Microanalysis found C 49.05 H 6.88 N 15.32 $C_{15}H_{25}Cl_3N_4$ requires C 48.99 H 6.85 N 15.24.

Example 28

N-Adamantan-1-yl-methyl-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 3-buten-1-ol replacing 4-penten-1-ol in step a, and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 7.94 (1H, br s), 7.65 (1H, br s), 7.57 (2H, m), 3.53-3.48 (2H, m), 3.29-3.24 (2H, m), 3.17-3.12 (2H, m), 2.99-2.93 (2H, m), 2.83 (2H, d, 5.7), 1.98-1.87 (9H, m), 1.69-1.56 (6H, m), 1.49 (6H, br s). Microanalysis found C 52.99 H 9.57 N 12.92. $C_{19}H_{36}Cl_2N_4$-$2H_2O$ requires C 53.39 H 9.43 N 13.11.

Example 29

N- Adamantan-1-yl-methyl-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.86 (1H, br s), 7.92 (1H, br s), 7.67 (1H, br s), 7.52 (2H, br s), 3.51-3.46 (2H, m), 3.20-3.06 (4H, m), 3.00-2.91 (2H, m), 2.83 (2H, d, 5.7), 2.00-1.84 (7H, m), 1.77-1.50 (16H, m). Microanalysis found C 54.25 H 9.72 N 12.46. $C_{20}H_{38}Cl_2N_4$-$2H_2O$ requires C 54.41 H 9.59 N 12.69.

Example 30

N- Adamantan-1-yl-methyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.80 (1H, br s), 7.84 (1H, br s), 7.63 (1H, br s), 7.49 (2H, br s), 3.49-3.44 (2H, m), 3.17-3.90 (6H, m), 2.82 (2H, d, 5.7), 1.94-1.86 (7H, m), 1.73-1.49 (16H, m), 1.40-1.35 (2H, m). Microanalysis found C 54.09 H 9.77 N 12.01. $C_{21}H_{40}Cl_2N_4$-$2.6H_2O$ requires C 54.09 H 9.77 N 12.01.

Example 31

N- Adamantan-1-yl-methyl-N'-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

The title compound was prepared as Example 17 with 6-hepten-1-ol replacing 4-penten-1-ol in step a and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.91 (1H, br s), 7.86 (1H, br s), 7.69 (1H, br s), 7.49 (2H, br s), 3.48-3.43 (2H, m), 3.16-3.02 (4H, m), 2.96-2.90 (2H, m), 2.84 (2H, d, 6), 1.98-1.84 (7H, m), 1.68-1.49 (16H, m), 1.32 (4H, br s). Microanalysis found C 56.07 H 9.89 N 11.88. $C_{22}H_{42}Cl_2N_4$-$2H_2O$ requires C 56.28 H 9.88 N 11.93.

Example 32

N-Adamantan-1-yl-methyl-N'-(7-pyrrolidin-1-yl-heptyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 7-octen-1-ol replacing 4-penten-1-ol in step a and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.85 (1H, br s), 7.81 (1H, br s), 7.65 (1H, br s), 7.47 (2H, br s), 3.48-3.43 (2H, m), 3.16-2.89 (6H, m), 2.84 (2H, d, 6), 1.98-1.83 (7H, m), 1.68-1.56 (8H, m), 1.48 (8H, br s), 1.29 (6H, m). Microanalysis found C 58.15 H 10.30 N 11.84. $C_{23}H_{44}Cl_2N_4$-$1.66H_2O$ requires C 57.86 H 9.99 N 11.73.

Example 33

N-(2-Adamantan-1-yl-ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 2-adamantan-1-yl-ethanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 10.94 (1H, br s), 7.79 (1H, br s), 7.55 (1H, br s), 7.49 (2H, br s), 3.50-3.49 (2H, m), 3.30-3.24 (2H, m), 3.14-3.11 (4H, m), 2.9-2.94 (2H, m), 1.98-1.86 (9H, m), 1.70-1.58 (6H, m), 1.49-1.39 (6H, m), 1.32-1.27 (2H). Microanalysis found C 56.35 H 9.69 N 13.28. $C_{20}H_{38}Cl_2N_4$-H_2O requires C 56.73 H 9.52 N 13.23.

Example 34

N-(3-Adamantan-1-yl-propyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 3-adamantan-1-yl-propanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 10.97 (1H, br s), 7.82 (1H, br s), 7.70 (1H, br s), 7.50 (2H, br s), 3.53-3.46 (2H, m), 3.28-3.24 (2H, m), 3.16-3.07 (4H, m), 3.01-2.91 (2H, m), 1.98-1.86 (9H, m), 1.68-1.56 (6H, m), 1.47-1.43 (8H, m), 1.06-1.01 (2H, m). Microanalysis found C 59.69 H 10.00 N 13.04. $C_{21}H_{40}Cl_2N_4$-$0.28H_2O$ requires C 59.41 H 9.63 N 13.20.

Example 35

N-(2-Adamantan-1-yl-ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a *2-Pent-4-enyl-isoindole-1,3-dione*. The potassium derivative of phthalimide (7.11g, 38.4mmol) and 5-bromo-1-pentene (5.00ml, 42.2mmol) in DMF (100ml) were heated at 70°C for 2h. The reaction mixture was allowed to cool to ambient temperature and diluted with ethyl acetate (100ml). The organic phase was washed sequentially twice with water (250ml) and brine (250ml) and was dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to give the title compound (6.44g, 78%). ^{1}H NMR 7.86-7.82 (2H, m), 7.74-7.70 (2H, m), 5.87-5.78 (1H, m), 5.10-4.96 (2H, m), 3.71 (2H, t, 7.2), 2.16-2.05 (2H, m), 1.85-1.75 (2H, m).

Step b *4-(1,3-Dioxo-1,3-dihydro-isoindol-2-yl)-butyraldehyde.* The title compound was prepared as in Example 17 step c with the product from Example 35 step a

replacing the product of Example 17 step b. ^{1}H NMR 9.78 (1H, t, 1.2), 7.88-7.82 (2H, m), 7.76 (2H, m), 3.77-3.72 (2H, m), 2.57-2.52 (2H, m), 2.05-2.00 (2H, m).

Step c *2-(4-Pyrrolidin-1-yl-butyl)-isoindole-1,3-dione.* The title compound was prepared as in Example 17 step d with the product from Example 35 step b replacing the product of Example 17 step c. ^{1}H NMR 7.85-7.80 (2H, m), 7.73-7.68 (2H, m), 3.71 (2H, t, 7.2), 2.49-2.44 (6H, m), 1.78-1.68 (6H, m), 1.61-1.51 (2H, m).

Step d *4-Pyrrolidin-1-yl-butylamine.* A solution of the product from step c (4.32g, 15.9mmol) and hydrazine hydrate (3.85ml, 79.4mmol) in ethanol (75ml) was heated at reflux for 1.5h. The resultant white suspension was diluted with further ethanol (50ml) and the solid removed by filtration. The filtrate was evaporated at reduced pressure and the residue was suspended in chloroform (50ml). The solid was removed by filtration and the filtrate evaporated at reduced pressure to afford the title compound (1.91g, 85%). ^{1}H NMR 2.74-2.69 (2H, m), 2.52-2.42 (6H, m), 1.83-1.75 (4H, m), 1.64-1.46 (6H, m).

Step e *N-(2-Adamantan-1-yl-ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 3 with 2-adamantan-1-yl-ethanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.96 (1H, br s), 7.83 (1H, br s), 7.60 (1H, br s), 7.47 (2H, br s), 3.49-3.44 (2H, m), 3.19-3.04 (6H, m), 2.97-2.95 (2H, m), 1.97-1.87 (7H, m), 1.76-1.48 (16H, m), 1.30-1.25 (2H). Microanalysis found C 57.79 H 9.88 N 12.83. $C_{21}H_{40}Cl_2N_4$-H_2O requires C 57.65 H 9.68 N 12.81.

Example 36

N-(3-Adamantan-1-yl-propyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with 3-adamantan-1-yl-propanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.98 (1H, br s), 7.85 (1H, br s), 7.73 (1H, br s), 7.49 (2H, br s), 3.47-3.45 (2H, m), 3.17-2.95 (8H, m), 1.96-1.43 (25H, m), 1.06-1.01 (2H,m). Microanalysis found C 58.71 H 10.24 N 12.16. $C_{22}H_{42}Cl_2N_4$-H_2O requires C 58.52 H 9.82 N 12.41.

Example 37

N-(2-Adamantan-1-yl-ethyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 35 with 6-bromo-1-hexene replacing 5-bromo-1-pentene in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 7.80 (1H, br s), 7.50 (1H, br s), 7.43 (2H, br s), 3.47-3.43 (4H, m), 3.14-2.94 (6H, m), 1.98-1.86 (7H, m), 1.69-1.25 (20H, m). Microanalysis found C 57.71 H 10.28 N 11.89. $C_{22}H_{42}Cl_2N_4$-1.4H_2O requires C 57.60 H 9.84 N 12.21.

Example 38

N-(3-Adamantan-1-yl-propyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with 3-adamantan-1-yl-propanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.84 (1H, br s), 7.72 (1H, br s), 7.64 (1H, br s), 7.43 (2H, br s), 3.47-3.45 (2H, m), 3.14-3.04 (6H, m), 2.96-2.94 (2H, m), 1.97-1.91 (7H, m), 1.69-1.34 (20H, m), 1.06-1.00 (2H,m). Microanalysis found C 59.42 H 10.17 N 12.22. $C_{23}H_{44}Cl_2N_4$-H_2O requires C 59.34 H 9.96 N 12.03.

Example 39

N-Cyclohexyl-methyl-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 3-buten-1-ol replacing 4-penten-1-ol in step a, and cyclohexyl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 7.82 (1H, br s), 7.71 (1H, br s), 7.50 (2H, m), 3.56-3.48 (2H, m), 3.29-3.23 (2H, m), 3.16-3.11 (2H, m), 3.00-2.93 (4H, m), 1.98-1.83 (6H, m), 1.71-1.67 (5H, m), 1.47-1.46 (1H, m), 1.21-1.08 (3H, m), 0.95-0.84 (2H). Microanalysis found C 48.04 H 9.69 N 14.98. $C_{15}H_{32}Cl_2N_4$-2H_2O requires C 48.00 H 9.67 N 14.93.

Example 40

N-Cyclohexyl-methyl-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with cyclohexyl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6)11.0 (1H, br s), 7.90

(1H, br s), 7 80 (1H, br s), 7.51 (2H, m), 3.50-3.45 (2H, m), 3.20-3.07 (4H, m), 3.00-2.96 (4H, m), 1.97-1 85 (4H, m), 1.72-1.45 (10H, m), 1.20-1.08 (3H, m), 0.95-0.87 (2H, m). Microanalysis found C 48.40 H 9.90 N 13.96. $C_{16}H_{34}Cl_2N_4$-2.5H_2O requires C 48.23 H 9.87 N 14.06.

Example 41

N-Cyclohexyl-methyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and cyclohexyl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 7.78 (1H, br s), 7.72 (1H, br s), 7.45 (2H, m), 3.50-3.44 (2H, m), 3.17-2.90 (8H, m), 1.99-1.83 (4H, m), 1.70-1.63 (7H, m), 1.51-1.31 (5H, m), 1.20-1.06 (3H, m), 0.95-0.87 (2H, m). Microanalysis found C 55.57 H 9.88 N 15.25. $C_{17}H_{36}Cl_2N_4$ requires C 55.28 H 10.03 N 14.97.

Example 42

N-(2-Cyclohexyl-ethyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 2-cyclohexyl-ethanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 10.92 (1H, br s), 7.78 (1H, br s), 7.64 (1H, br s), 7.49 (2H, br s), 3.50-3.46 (2H, m), 3.28-3.25 (2H, m), 3.14-3.12 (4H, m), 2.99-2.96 (2H, m), 1.98-1.86 (6H, m), 1.68-1.65 (5H, m), 1.47-1.09 (6H, m), 0.93-0.86 (2H, m). Microanalysis found C 49.49 H 10.18 N 14.44. $C_{16}H_{34}Cl_2N_4$-2H_2O requires C 49.35 H 9.84 N 14.39.

Example 43

N-(3-Cyclohexyl-propyl)-N'-(3-pyrrolidin-1-yl-propyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with 3-cyclohexyl-propanol replacing 4-methoxybenzyl alcohol in step a. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 7.92 (1H, br s), 7.81 (1H, br s), 7.56 (2H, br s), 3.48-3.47 (2H, m), 3.29-3.24 (2H, m), 3.17-3.06 (4H, m), 2.99-2.97 (2H, m), 1.97-1.86 (6H, m), 1.67-1.63 (5H, m), 1.49-1.44 (2H, m), 1.19-1.05 (6H,m), 0.89-0.82 (2H, m). Microanalysis found C 53.14 H 10.16 N 14.28. $C_{17}H_{36}Cl_2N_4$-H_2O requires C 52.98 H 9.94 N 14.54.

Example 44

N-(1(R)-Cyclohexyl-ethyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 17 with 1-(R)-cyclohexyl-ethylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6)10.9 (1H, br s), 7.80 (1H, br s), 7.58 (1H, d, 9), 7.46 (2H, m), 3.48-3.46 (3H, m), 3.20-3.06 (4H, m), 2.97-2.91 (2H, m), 1.97-1 85 (4H, m), 1.76-1.49 (9H, m), 1.30-0.91 (9H, m). Microanalysis found C 50.49 H 10.14 N 13.66. $C_{17}H_{36}Cl_2N_4$-$2H_2O$ requires C 50.61 H 9.99 N 13.89.

Example 45

N-(1(S)-Cyclohexyl-ethyl)-N'(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 1-(S)-cyclohexyl-ethylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6)10.9 (1H, br s), 7.80 (1H, br s), 7.58 (1H, d, 9), 7.46 (2H, m), 3.48-3.46 (3H, m), 3.20-3.06 (4H, m), 2.97-2.91 (2H, m), 1.97-1.85 (4H, m), 1.76-1.49 (9H, m), 1.30-0.91 (9H, m). Microanalysis found C 50.49 H 10.14 N 13.66. $C_{17}H_{36}Cl_2N_4$-$2H_2O$ requires C 50.61 H 9.99 N 13.89.

Example 46

N-Cycloheptyl-methyl-N'(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with cycloheptyl-methanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine repalcing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.88 (1H, br s), 7.78-7.74 (2H, m), 7.46 (2H, s), 3.50-3.44 (2H, m), 3.17-2.94 (8H, m), 1.99-1.83 (4H, m), 1.70-1.38 (17H, m), 1.19-1.09 (2H, m). Microanalysis found C 47.74 H 10.45 N 12.33. $C_{18}H_{38}Cl_2N_4$-$4H_2O$ requires C 47.67 H 10.22 N 12.35.

Example 47

N-Benzyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and benzylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.7 (1H, br s), 8.09 (1H, br s), 7.85 (1H, br s), 7.56 (2H, br s), 7.40-7.27 (5H, m), 4.43 (2H, d, 6), 3.47-3.46 (2H, m), 3.17-2.92 (6H, m), 1.97-1.86 (4H, m), 1.66 (2H, m), 1.49-1.46 (2H, m), 1.33-1.30 (2H, m). Microanalysis found C 51.62 H 8.71 N 14.25. $C_{17}H_{30}Cl_2N_4$-$2H_2O$ requires C 51.38 H 8.62 N 14.10.

Example 48

N-(2-Methylbenzyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and 2-methylbenzylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 8.02 (2H, br s), 7.64 (2H, br s), 7.20 (4H, m), 4.40 (2H, d, 6), 3.46-3.43 (2H, m), 3.20-3.18 (2H, m), 3.05-2.93 (4H, m), 2.28 (3H, s), 1.96-1.87 (4H, m), 1.68 (2H, m), 1.51-1.48 (2H, m), 1.36-1.30 (2H, m). Microanalysis found C 48.48 H 8.98 N 12.33. $C_{18}H_{32}Cl_2N_4$-$4H_2O$ requires C 48.32 H 9.01 N 12.52

Example 49

N-(1(S)-Phenyl-ethyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and 1-(S)-phenylethylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.8 (1H, br s), 8.35 (1H, br s), 7.90 (1H, br s), 7.58 (2H, br s), 7.40-7.24 (5H, m), 4.94-4.86 (1H, m), 3.46-3.43 (2H, m), 3.13-2.91 (6H, m), 1.96-1.86 (4H, m), 1.63 (2H, m), 1.41-1.39 (5H, m), 1.24 (2H, m). Microanalysis found C 52.49 H 8.73 N 13.41. $C_{18}H_{32}Cl_2N_4$-$2H_2O$ requires C 52.55 H 8.82 N 13.62.

Example 50

N-Benzyl-N-methyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

Step a *N,N'-Bis(*tert*-butoxycarbonyl)-N''-benzyl-N''-methyl-guanidine.* To an ice-cooled solution of N-benzylmethylamine (1.94ml, 15.0mmol) in DCM (90ml) was added sequentially triethylamine (6.26ml, 45.0mmol), 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopseudourea (2.90g, 10.0mmol) and mercury (II) chloride (2.72g, 10.0mmol). The coolant was removed and the resultant suspension was stirred at ambient temperature for 72h. The suspension was filtered through a plug of celite and the filter-cake was washed with further DCM (20ml). The filtrate was washed sequentially with 10% aqueous citric acid (100ml), 10% aqueous potassium carbonate (100ml) and brine (100ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate was evaporated at reduced pressure. The crude residue was purified by flash column chromatography (3:1 hexane ethyl acetate) to afford the title compound (3.02g, 83%). ^{1}H NMR 10.17 (1H, br s), 7.38-7.27 (5H, m), 4.71 (2H, br s), 2.90 (3H, s), 1.52 (9H, s), 1.50 (9H, s).

Step b *N,N'-Bis(*tert-*butoxycarbonyl)-N-(5-bromo-pentyl)-N''-benzyl-N'''-methyl-guanidine.* To an ice-cooled solution of the product from step a (1.07g, 2.95mmol) in DMF (10ml) was added sodium hydride (60% dispersion in mineral oil, 141mg, 3.58mmol) in a single portion. The coolant was removed and the suspension was stirred at ambient temperature for 20 minutes. The suspension was re-cooled in ice and treated in a single portion with 1,5-dibromopentane (1.20ml, 8.81mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 18h. The reaction was quenched with water (50ml) and extracted with ethyl acetate (40ml). The aqueous phase was discarded and the organic phase washed twice with brine (40ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the crude residue purified by flash column chromatography (3:1 hexane ethyl acetate) to afford the title compound (1.24g, 82%).

Step c *N,N'-Bis(*tert-*butoxycarbonyl)-N''-benzyl-N'''-methyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine.* To an ice-cooled solution of the product from step b (1.24g, 2.42mmol) in acetonitrile (6ml) was treated with pyrrolidine (0.404ml, 4.84mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 18h. The solvent was evaporated at reduced pressure and the crude residue was purified by flash column chromatography (100:10:1 DCM:methanol:ammonia) to afford the title compound (1.14g, 94%).

Step d *N-Benzyl-N-methyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 50 step c replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 7.84 (1H, br s), 7.75 (2H, br s), 7.42-7.19 (5H, m), 4.66 (2H, s), 3.45-3.41 (2H, m), 3.24-3.22 (2H, m), 3.03-2.93 (7H, m), 1.96-1.89 (4H, m), 1.68 (2H, m), 1.51-1.49 (2H, m), 1.30-1.28 (2H, m). Microanalysis found C 50.22 H 9.04 N 13.07. $C_{18}H_{32}Cl_2N_4$-$3H_2O$ requires C 50.34 H 8.92 N 13.05.

Example 51

*N-(5-Pyrrolidin-1-yl-pentyl)-3,4-dihydro-1*H*-isoquinoline-2-carboxamidine bis-hydrochloride.*

The title compound was prepared as in Example 50 with tetrahydroisoquinoline replacing N-benzylamine in step a. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 8.01 (1H, br s), 7.83 (2H, br s), 7.22-7.15 (4H, m), 4.62 (2H, s), 3.65 (2H, t, 6), 3.46-3.44 (2H, m), 3.25-3.24 (2H, m), 3.06-3.03 (2H, m), 2.92-2.88 (4H, m), 1.96-1.89 (4H, m), 1.70 (2H,

m), 1.56 (2H, m), 1.35 (2H, m). Microanalysis found C 54.14 H 8.66 N 12.99. $C_{19}H_{32}Cl_2N_4$-$2H_2O$ requires C 53.92 H 8.57 N 13.24.

Example 52

N,N'-Bis-(4-Chlorobenzyl)-N-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a *(4-Chlorobenzyl)-carbamic acid* tert-*butyl ester.* To a stirred solution of 4-chlorobenzylamine (9.86g, 69.6mmol) in 1,4-dioxan (100ml) was added dropwise a solution of di-*tert*-butyldicarbonate (15.2g, 69.6mmol) in 1,4-dioxan (50ml). The solution was stirred at ambient temperature for 45 minutes and then the solvent was evaporated at reduced pressure. The residue was suspended in hexane (300ml) and the solid recovered by filtration. The solid was washed with further hexane (50ml) and dried *in vacuo* at 50°C to afford the title compound (13.5g, 80%). ^{1}H NMR 7.31-7.20 (4H, m), 4.80 (1H, br s), 4.27 (2H, d, 5.7), 1.46 (9H, s).

Step b *(4-Chlorobenzyl)-pent-4-enyl-carbamic acid* tert *butyl ester.* The title compound was prepared as in Example 35 step a with the product from Example 52 step a replacing the potassium derivative of phthalimide. ^{1}H NMR 7.31 (2H, d, 7.8), 7.18 (2H, d, 7.8), 5.84-5.71 (1H, m), 5.04-4.95 (2H, m), 4.39 (2H br s), 3.16 (2H, br s), 2.05-1.98 (2H, m), 1.62-1.57 (2H, m), 1.47 (9H, s).

Step c *(4-Chlorobenzyl)-pent-4-enyl-amine bis-hydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 52 step b replacing the product of Example 2 step b. ^{1}H NMR 9.57 (2H, br s), 7.64 (2H, d, 8.4), 7.49 (2H, d, 8.4), 5.83-5.70 (1H, m), 5.07-4.96 (2H, m), 4.10 (2H, s), 2.84-2.79 (2H, m), 2.10-2.03 (2H, m), 1.81-1.71 (2H, m).

Step d *N-(4-Chlorobenzyl)-N',N''-bis(*tert-*butoxycarbonyl)-N-pent-4-enyl-guanidine.* The title compound was prepared as in Example 50 step a with the product from Example 52 step c replacing N-benzylmethylamine.

Step e *N-N'-Bis-(4-Chlorobenzyl)-N',N''-bis(*tert-*butoxycarbonyl)-N-pent-4-enyl-guanidine.* The title compound was prepared as in Example 2 step a with the product from Example 52 step d replacing 1,3-bis(*tert*-butoxycarbonyl)-2-methyl-2-thiopsuedourea.

Step f *N-N'-Bis-(4-Chlorobenzyl)-N',N''-bis(*tert-*butoxycarbonyl)-N-(4-oxo-butyl)-guanidine.* The title compound was prepared as in Example 17 step c with the product from Example 52 step e replacing the product of Example 17 step b.

Step g *N-N'-Bis-(4-Chlorobenzyl)-N',N''-bis(*tert-*butoxycarbonyl)-N-(4-pyrrolidin-1-yl-butyl)-guanidine.* The title compound was prepared as in Example 17 step d with the product from Example 52 step f replacing the product of Example 17 step c.

Step h *N,N'-Bis-(4-Chlorobenzyl)-N-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 2 step cwith the product from Example 52 step g replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 8.66 (1H, br s), 7.93-7.92 (2H, br s), 7.44-7.21 (8H, m), 4.75 (2H, s), 4.51-4.49 (2H, m), 3.44 (4H, br s), 3.06-3.04 (2H, m), 2.90 (2H, m), 1.95-1.86 (4H, m), 1.64 (4H, br s). Microanalysis found C 49.28 H 6.41 N 9.79. $C_{23}H_{32}Cl_4N_4$-$3H_2O$ requires C 49.30 H 6.83 N 10.00.

Example 53

N-(Naphthalen-2-yl-methyl)-N'-(5-pyrrolidin-1-yl-pentyl)guanidine bis-hydrochloride. The title compound was prepared as in Example 2 with 2-bromomethylnaphthalene replacing 4-chlorobenzyl bromide in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 8.34 (1H, br s), 8.03 (1H, br s), 8.01-7.83 (4H, m), 7.67 (2H, br s), 7.53-7.45 (3H, m), 4.61 (2H, d, 6), 3.45-3.43 (2H, m), 3.21-3.19 (2H, m), 2.99 –2.89(4H, m), 1.94-1.85 (4H, m), 1.65 (2H, m), 1.49-1.47 (2H, m), 1.32-1.29 (2H, m). Microanalysis found C 56.11 H 8.06 N 12.67. $C_{21}H_{32}Cl_2N_4$-$2H_2O$ requires C 56.37 H 8.11 N 12.52.

Example 54

N-Biphenyl-4-yl-methyl-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with biphenyl-4-yl-methanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 8.31 (1H, br s), 8.07 (1H, br s), 7.68-7.64 (6H, m), 7.48-7.33 (5H, m), 4.50 (2H, d, 6), 3.45-3.43 (2H, m), 3.23-3.21 (2H, m), 3.11-3.07 (2H, m), 2.92 (2H, m), 1.97-1.85 (4H, m), 1.70 (2H, m), 1.56-1.54 (2H, m). Microanalysis found C 57.72 H 7.89 N 12.24. $C_{22}H_{32}Cl_2N_4$-$1.88H_2O$ requires C 57.78 H 7.88 N 12.25.

Example 55

N-Biphenyl-4-yl-methyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with biphenyl-4-yl-methanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10 9 (1H, br s), 8.29 (1H, br s), 8.01 (1H, br s), 7.68-7.65 (6H, m), 7.48-7.33 (5H, m), 4.49 (2H, d, 6), 3.51-3.41 (2H, m), 3.22-3.16 (2H, m), 3.05-2.98 (2H, m), 2.92-2.87 (2H, m), 1.94-1.83 (4H, m), 1.72-1.62 (2H, m), 1.52-1.45 (2H, m), 1.33-1.31 (2H, m). Microanalysis found C 58.13 H 8.13 N 11.88. $C_{23}H_{34}Cl_2N_4$-$2H_2O$ requires C 58.34 H 8.09 N 11.83.

Example 56

N-(4-Cyclohexylbenzyl)-N'-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 3 with (4-cyclohexylphenyl)-methanol replacing 4-methoxybenzyl alcohol in step a, and 4-pyrrolidin-1-yl-butylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 8.21 (1H, br s), 8.06 (1H, br s), 7.65 (2H, br s), 7.25 (2H, d, 6), 7.18 (2H, d, 6), 4.39 (2H, d, 6), 3.45-3.44 (2H, m), 3.21-3.19 (2H, m), 3.11-3.07 (2H, m), 2.94 (2H, m), 1.96-1.23 (19H, m). Microanalysis found C 56.75 H 9.23 N 11.88. $C_{22}H_{38}Cl_2N_4$-$2H_2O$ requires C 56.76 H 9.09 N 12.04.

Example 57

N-(4-Cyclohexylbenzyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 3 with (4-cyclohexylphenyl)-methanol replacing 4-methoxybenzyl alcohol in step a, and 5-pyrrolidin-1-yl-pentylamine replacing 3-pyrrolidin-1-yl-propylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 8.13 (1H, br s), 7.93 (1H, br s), 7.59 (2H, br s), 7.24-7.18 (4H, m), 4.38 (2H, d, 6), 3.50-3.43 (2H, m), 3.20-3.13 (2H, m), 3.08-2.92 (4H, m), 2.49 (1H, m), 1.99-1.63 (11H, m), 1.51-1.23 (9H, m). Microanalysis found C 56.38 H 9.33 N 11.48. $C_{23}H_{40}Cl_2N_4$-$2.5H_2O$ requires C 56.55 H 9.28 N 11.47.

Example 58

N-(5-Pyrrolidin-1-yl-pentyl)-N'-(tetrahydro-pyran-2-yl-methyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and tetrahydro-pyran-2-yl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 7.74 (1H, br s),

7.52 (1H, br s), 7.46 (2H, br s), 3.90-3.86 (1H, m), 3.47-3.03 (12H, m), 1.96-1.33 (16H, m). Microanalysis found C 48.40 H 9.61 N 13.88. $C_{16}H_{34}Cl_2N_4O$-1.5H_2O requires C 48.48 H 9.41 N 14.13.

Example 59

N-Adamantan-1-yl-methyl-N'-(2-(2-pyrrolidin-1-yl-ethoxy)-ethyl)-guanidine bis-hydrochloride.

The title compound was prepared as in Example 17 with 2-allyloxy-ethanol replacing 4-penten-1-ol in step a, and adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.4 (1H, br s), 8.06 (1H, br s), 7.75 (1H, br s), 7.65 (2H, br s), 3.75-3.72 (2H, m), 3.55-3.53 (4H, m), 3.41-3.34 (4H, m), 3.07-3.04 (2H, m), 2.88 (2H, d, 5.7), 1.94 (7H, br s), 1.68-1.51 (12H, m). Microanalysis found C 57.07 H 8.96 N 13.18. $C_{20}H_{38}Cl_2N_4O$ requires C 57.00 H 9.09 N 13.29.

Example 60

N- Adamantan-1-yl-methyl-N'-(5-piperidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b, and piperidine replacing pyrrolidine in step d. ^{1}H NMR (DMSO-d_6) 10.44 (1H, br s), 7.89 (1H, br s), 7.68 (1H, br s), 7.51 (2H, br s), 3.32 (3H, br s), 3.15 (2H, q, 6.3), 2.94 (2H, m), 2.83 (4H, m), 1.93 (3H ,br s), 1.83-1.45 (20H, m), 1.34 (3H, m). Microanalysis found C 52.28 H 9.90 N 11.03. $C_{22}H_{42}Cl_2N_4$-4H_2O requires C 52.27 H 9.97 N 11.08.

Example 61

N-Adamantan-1-yl-methyl-N'-(5-azepan-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b, and hexamethyleneimine replacing pyrrolidine in step d. ^{1}H NMR (DMSO-d_6) 10.54 (1H, br s), 7.88 (1H, br s), 7.67 (1H, br s), 7.50 (2H, br s), 3.29 (2H, br s), 3.15 (2H, q, 6.4), 3.02 (4H, m), 2.83 (2H, d, 6), 1.94 (3H ,br s), 1.80-1.40 (24H, m), 1.34 (2H, m). Microanalysis found C 53.01 H 10.17 N 10.40. $C_{23}H_{44}Cl_2N_4$-4H_2O requires C 53.17 H 10.09 N 10.78.

Example 62

N-Adamantan-1-yl-methyl-N'-(5-azocan-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b, and heptamethyleneimine replacing pyrrolidine in step d. ^{1}H NMR (DMSO-d_6) 10.50 (1H, br s), 7.88 (1H, br s), 7.66 (1H, br s), 7.50 (2H, br s), 3.30 (2H, br s), 3.16-2.98 (6H, m), 2.83 (2H, d, 6), 1.94 (3H ,br s), 1.83-1.40 (26H, m), 1.34 (2H, m). Microanalysis found C 54.00 H 10.32 N 10.43. $C_{24}H_{46}Cl_2N_4$-$4H_2O$ requires C 54.02 H 10.20 N 10.50.

Example 63

N-Adamantan-1-yl-methyl-N'-(5-(4-methyl-piperazin-1-yl)-pentyl)-guanidine tris-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step b, and 1-methyl-piperazine replacing pyrrolidine in step d. ^{1}H NMR (DMSO-d_6) 12.0 (2H, br s), 7.86 (1H, br s), 7.67 (1H, br s), 7.50 (2H, br s), 3.75-3.25 (8H, m), 3.14 (4H, m), 2.84-2.80 (5H, m), 1.94 (3H ,br s), 1.73-1.40 (16H, m), 1.35 (2H, m). Microanalysis found C 50.70 H 9.52 N 13.49. $C_{22}H_{44}Cl_3N_5$-$2H_2O$ requires C 50.72 H 9.29 N 13.44.

Example 64

N-(4-Chlorobenzyl)-N'-methyl-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.

Step a *1-(4-Chlorobenzyl)-3-methyl-thiourea.* To an ice-cooled aqueous solution of methylamine (40%w/w, 10ml) was added a solution of 4-chlorobenzylisocyanate (1.84g, 10.0mmol) in 1,4-dioxan (10ml). The coolant was removed and the reaction was stirred at ambient temperature for 1h. The reaction mixture was partitioned between ethyl acetate (40ml) and water (40ml). The aqueous phase was discarded and the organic phase washed with brine (40ml), and was dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound (2.02g, 94%). ^{1}H NMR 7.91 (1H, br m), 7.52 (1H, br m), 7.39-7.28 (4H, m), 4.62 (2H, d, 3.9), 2.82 (3H, bd, 2.4).

Step b *1-(4-Chlorobenzyl)-2,3-dimethyl-isothiourea iodide.* A solution of the product of step a (2.00g, 9.27mmol) and iodomethane (0.866ml, 13.9mmol) in acetone (20ml) was heated at reflux for 2h. The reaction mixture was cooled in ice to give rise to a white precipitate. The solid was isolated by filtration and the solid was washed with cold acetone to afford the title compound (2.92g, 88%). ^{1}H NMR (DMSO-d_6) 9.80-8.80 (2H, br m), 7.46 (2H, d, 8.7), 7.35 (2H, d, 8.7), 4.58 (2H, s), 3.00-2.95 (3H, br s), 2.70-2.59 (3H, br s).

Step c *N-(4-Chlorobenzyl)-N'-methyl-N''-(3-pyrrolidin-1-yl-propyl)-guanidine.* A solution of the product from step b (358mg, 1.00mmol) and 3-pyrrolidin-1-yl-propylamine (0.19ml) in ethanol (4ml) was stirred at ambient temperature for 16h followed by heating at reflux for 1h. The solvent was removed at reduced pressure and the residue was partitioned between DCM (20ml) and aqueous ammonia (880, 20ml). The aqueous phase was extracted with further DCM (10ml) and then discarded. The combined organic phases were washed twice with water (20ml) and once with brine (20ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated to afford the title compound (225mg, 73%). ^{1}H NMR 7.40-7.29 (4H, m), 4.60 (2H, s), 3.42-3.47 (2H, m), 2.97 (3H, s), 2.50-2.44 (6H, m), 1.83-1.63 (6H, m).

Example 65

N-Butyl-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine.

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and n-butylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR 3.15 (4H, br m), 2.43-2.34 (6H, br m), 1.74 (4H, br s), 1.56-1.42 (6H, m), 1.35-1.28 (4H, m), 0.86 (3H, t, 7.2). The title compound was converted to the bis-maleic acid salt and lyophilised from 1,4-dioxan and water.

Example 66

N-(3-Methyl-butyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and *iso*-amylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H ,br s), 7.79 (1H, br s), 7.69 (1H, br s), 7.47 (2H, br s), 3.50-3.43 (2H, m), 3.16-2.90 (8H, m), 1.99-1.85 (4H, m), 1.73-1.32 (9H, m), 0.88 (6H, d, 6.6).

Example 67

N-(2-Methyl-butyl)-N'-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 17 with 5-hexen-1-ol replacing 4-penten-1-ol in step a, and 2-methyl-butylamine replacing 4-chlorobenzylamine in step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H ,br s), 7.85 (1H, br s), 7.75 (1H, br s), 7.50 (2H, br s), 3.50-3.44 (2H, m), 3.15-2.90 (8H, m), 1.99-1.83 (4H, m), 1.73-1.34 (8H, m), 1.56-1.06 (1H, m), 0.87-0.82 (6H, m).

Example 68

N-(4-Chlorobenzyl)-N-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride

Step a *(4-Chlorobenzyl)-(4-oxo-butyl)-carbamic acid tert-butyl ester.* The title compound was prepared as in Example 17 step c with the product from Example 52 step b replacing the product of Example 17 step b. ^{1}H NMR 9.75 (1H, m),. 7.29 (2H, d, 8.1), 7.15 (2H, d, 8.1), 4.39 (2H, s), 3.21 (2H, br s), 2.43 (2H, br s), 1.85-1.80 (2H, m), 1.47 (9H, s).

Step b *(4-Chlorobenzyl)-(4-pyrrolidin-1-yl-butyl)-carbamic acid tert-butyl ester.* The title compound was prepared as in Example 17 step d with the product from Example 68 step a replacing the product of Example 17 step c. ^{1}H NMR 7.30-7.27 (2H, m), 7.17-7.15 (2H, m), 4.38 (2H, br s), 3.21 (2H, br m), 2.52 (6H, br s), 1.81 (4h, br s), 1.46 (13H, m).

Step c *(4-Chlorobenzyl)-(4-pyrrolidin-1-yl-butyl)-amine bis-hydrochloride.* The title compound was preapred as in Example 2 step c with the product from Example 68 step b replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, bs0, 9.50 (2H, br s), 7.61 (2H, d, 8.4), 7.48 (2H, d, 8.4), 4.11 (2H, s), 3.44 (2H, br s), 3.08-2.87 (6H, m), 1.92 (4H, br s), 1.73 (4H, br s).

Step d *N,N'-Bis(*tert*-butyoxycarbonyl)-N''-(4-chlorobenzyl)-N''-(4-pyrrolidin-1-yl-butyl)-guanidine*. The title compound was prepared as in Example 50 step a with the product from Example 68 step c replacing N-benzylmethylamine. ^{1}H NMR 9.97 (1H, br s), 7.32-7.22 (4H, m), 4.67 (2H, s), 3.34-3.29 (2H, m), 2.51-2.36 (6H, m), 1.76-1.70 (4H, m), 1.50-1.41 (22H, m).

Step e *N-(4-Chlorobenzyl)-N-(4-pyrrolidin-1-yl-butyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 68 step d replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6)

11.0 (1H, br s), 7.73 (4H, br s), 7.46 (2H, d, 6), 7.27 (2H, d, 6), 4.64 (2H, s), 3.47-3.28 (4H, m), 3.05-2.89 (4H, m), 1.95-1.86 (4H, m), 1.62-1.58 (4H, m). Microanalysis found C 45.72 H 7.49 N 13.40. $C_{16}H_{27}Cl_3N_4$-$2H_2O$ requires C 46.00 H 7.48 N 13.41.

Example 69

N-(4-Chlorobenzyl)-N-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

Step a *(5-Bromo-pentyl)-(4-chlorobenzyl)-carbamic acid tert-butyl ester.* To an ice-cooled stirred solution of the product from Example 52 step a (725mg, 3.00mmol) in DMF (9ml) was added, in a single portion, sodium hydride (60% dispersion in mineral oil, 144mg, 3.60mmol). The coolant was removed and the suspension was stirred at ambient temperature for 30 minutes. The suspension was cooled in ice and 1,5-dibromopentane (1.23ml, 9.03mmol) was added in three portions. The coolant was removed and the reaction mixture was stirred at ambient temperature for 18h. The reaction was quenched with water (40ml) and then extracted with ethyl acetate (40ml). The aqueous phase was discarded and the organic phase washed twice with brine (40ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (5:1 hexane:ethyl acetate) to afford the title product.

Step b *(4-Chlorobenzyl)-(5-pyrrolidin-1-yl-pentyl)-amine bis-hydrochloride.* To a stirred solution of the product from step a in acetonitrile (4ml) was added pyrrolidine (1.27ml, 15.2mmol). The solution was stirred at ambient temperature for 18h. The reaction mixture was diluted with ethyl acetate (50ml) and washed sequentially with water (50ml) and brine (50ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue treated with hydrogen chloride in 1,4-dioxan (10ml). The solution was stirred at ambient temperature for 1h and the solvent removed at reduced pressure to afford the title compound (655mg, 62%). ^{1}H NMR (DMSO-d_6) 12.1 (1H, br s), 10.8 (1H, br s), 9.47 (1H, br s), 7.64 (2H, d, 9), 7.53 (2H, d, 9), 4.10 (2H, s), 3.46-3.45 (2H, m), 3.06-2.85 (6H, m), 1.97-1.64 (8H, m), 1.37-1.35 (2H, m).

Step c *N,N'-Bis(*tert*-butyoxycarbonyl)-N''-(4-chlorobenzyl)-N''-(5-pyrrolidin-1-yl-pentyl)-guanidine*. The title compound was prepared as in Example 50 step a with the product from Example 69 step b replacing N-benzylmethylamine. ^{1}H NMR 9.95 (1H, br s), 7.32-7.22 (4H, m), 4.67 (2H, s), 3.32-3.27 (2H, m), 2.48-2.36 (6H, m), 1.78 (4H, br s), 1.60-1.42 (22H, m), 1.30-1.22 (2H, m).

Step d *N-(4-Chlorobenzyl)-N-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 2 step c with the product from Example 69 step c replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 7.67-7.61 (4H, br m), 7.46 (2H, d, 6), 7.27 (2H, d, 6), 4.62 (2H, s), 3.46-3.44 (2H, m), 3.27-3.24 (2H, m), 3.03-2.90 (4H, m), 1.96-1.86 (4H, m), 1.65-1.52 (4H, m), 1.30-1.27 (2H, m). Microanalysis found C 47.21 H 7.66 N 13.26. $C_{17}H_{29}Cl_3N_4$-$2H_2O$ requires C 47.28 H 7.70 N 12.97.

Example 70

N-(4-Chlorobenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,6-dibromohexane repalcing 1,5-dibromopentane in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 7.68 (4H, br s), 7.47 (2H, d, 9), 7.27 (2H, d, 9), 4.62 (2H, s), 3.48-3.38 (2H, m), 3.29-3.24 (2H, m), 3.05-2.88 (4H, m), 1.98-1.80 (4H, m), 1.66-1.58 (2H, m), 1.50 (2H, br s), 1.27-1.26 (4H, m). Microanalysis found C 49.47 H 7.72 N 12.83. $C_{18}H_{31}Cl_3N_4$-$1.5H_2O$ requires C 49.49 H 7.85 N 12.83.

Example 71

N-(4-Chlorobenzyl)-N-(7-pyrrolidin-1-yl-heptyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,7-dibromoheptane replacing 1,5-dibromopentane in step a . ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 7.72 (4H, br s), 7.46 (2H, d, 9), 7.27 (2H, d, 9), 4.62 (2H, s), 3.48-3.41 (2H, m), 3.26 (2H, t, 7.5), 3.05-2.86 (4H, m), 1.98-1.82 (4H, m), 1.64 (2H, m), 1.48 (2H, br m), 1.24 (6H, br s). Microanalysis found C 49.70 H 7.98 N 12.24. $C_{19}H_{33}Cl_3N_4$-$2H_2O$ requires C 49.62 H 8.11 N 12.18.

Example 72

N-(4-Chlorobenzyl)-N-(6-piperidin-1-yl-hexyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,6-dibromohexane replacing 1,5-dibromopentane in step a, and piperidine replacing pyrrolidine in step b. ^{1}H NMR (DMSO-d_6) 10.6 (1H, br s), 7.71 (4H, br s), 7.46-7.43 (2H, m), 7.27-7.25 (2H, m), 4.62 (2H, s), 3.38-3.24 (4H, m), 2.94-2.73 (4H, m), 1.89-1.24 (14H, m). Microanalysis found C 49.47 H 7.90 N 12.11. $C_{19}H_{33}Cl_3N_4$-$2H_2O$ requires C 49.62 H 58.11 N 12.18.

Example 73

N-Benzyl-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

Step a *Benzyl-carbamic acid tert-butyl ester.* The title compound was prepared as in Example 52 step a with benzylamine replacing 4-chlorobenzylamine. ^{1}H NMR 7.36-7.28 (5H, m), 4.83 (1H, br s), 4.33 (2H, d, 5.7), 1.47 (9H, s).

Step b *N-Benzyl-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 69 with the product from step a and 1,6-dibromohexane replacing respectively the product of Example 52 step a and 1,5-dibromopentane in step a. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 7.72 (4H, br s), 7.41-7.22 (5H, m), 4.62 (2H, s), 3.47-3.41 (2H, m), 3.29-3.24 (2H, m), 3.05-2.88 (4H, m), 1.98-1.79 (4H, m), 1.66-1.58 (2H, m), 1.49 (2H, br s), 1.26-1.25 (4H, m). Microanalysis found C 50.49 H 8.99 N 13.22. $C_{18}H_{32}Cl_2N_4$-$3H_2O$ requires C 50.34 H 8.92 N 13.05.

Example 74

N-(4-Bromobenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

Step a *(4-Bromobenzyl)-carbamic acid* tert-*butyl ester.* To a stirred suspension of 4-bromo-benzylamine hydrochloride (968mg, 4.35mmol) and triethylamine (0.666ml, 4.79mmol) in chloroform (15ml) was added di-*tert*-butyldicarbonate (949mg, 4.35mmol). The resulting solution was stirred at ambient temperature for 2h and then diluted with DCM (40ml). The organic solution was washed sequentially with 10% aqueous citric acid (40ml) and brine (40ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure to afford the title compound (1.23g, 99%). ^{1}H NMR 7.48-7.43 (2H, m), 7.18 (2H, d, 8.4), 4.84 (1H, br s), 4.27 (2H, d, 5.7), 1.46 (9H, s).

Step b *N-(4-Bromobenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 69 with the product from step a and 1,6-dibromohexane replacing respectively the product of Example 52 step a and 1,5-dibromopentane in step a. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 7.71 (4H, br s), 7.59 (2H, d, 9), 7.21 (2H, d, 9), 4.61 (2H, s), 3.46-3.24 (4H, m), 3.03-2.90 (4H, m), 1.95-1.84 (4H, m), 1.64 (2H, br s), 1.49 (2H, br s), 1.25 (4H, br s). Microanalysis found C 42.41 H 7.31 N 11.05. $C_{18}H_{31}BrCl_2N_4$-$3H_2O$ requires C 42.53 H 7.34 N 11.02.

Example 75

N-(1-(S)-Phenyl-ethyl)-N-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride

Step a *(1-(S)-Phenyl-ethyl)-carbamic acid* tert-*butyl ester.* The title compound was prepared as in Example 52 step a with 1-(S)-phenyl-ethylamine replacing 4-chlorobenzylamine. ^{1}H NMR 7.36-7.28 (5H, m), 4.78 (2H, br s), 1.47-1.43 (12H, m).

Step b *N-(1-(S)-Phenyl-ethyl)-N-(5-pyrrolidin-1-yl-pentyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 69 with the product from step a replacing the product of Example 52 step a in step a.. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 7.71 (4H, br s), 7.44-7.31 (5H, m), 5.34 (1H, q,. 6), 3.45-3.36 (2H, m), 3.16-2.84 (6H, m), 1.97-1.82 (4H, m), 1.62-1.05 (9H, m). Microanalysis found C 53.71 H 8.86 N 13.66. $C_{18}H_{32}Cl_2N_4$-1.5H_2O requires C 53.73 H 8.77 N 13.92.

Example 76

N-(2-Methylbenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

Step a *(2-Methylbenzyl)-carbamic acid* tert-*butyl ester.* The title compound was prepared as in Example 52 step a with 2-methylbenzylamine replacing 4-chlorobenzylamine. ^{1}H NMR 7.27-7.17 (4H, m), 4.60 (1H, br s), 4.33 (2H, d, 5.4), 2.34 (3H, s), 1.47 (9H, s).

Step b *N-(2-Methylbenzyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride.* The title compound was prepared as in Example 69 with the product form step a and 1,6-dibromohexane replacing respectively the product of Example 52 step a and 1,5-dibromopentane in step a. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 7.64 (4H, br s), 7.21-7.20 (3H, m), 6.95-6.94 (1H, m), 4.56 (2H, s), 3.45-3.36 (2H, m), 3.25-3.22 (2H, m), 3.03-2.91 (4H, m), 2.24 (3H, s), 1.95-1.85 (4H, m), 1.64-1.53 (4H, m), 1.27-1.26 (4H, m). Microanalysis found C 51.30 H 9.32 N 12.32. $C_{19}H_{34}Cl_2N_4$-3H_2O requires C 51.46 H 9.09 N 12.63.

Example 77

N-Adamantan-1-yl-methyl-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

Step a *Adamantane-1-carboxylic acid (6-hydroxy-hexyl)-amide.* To an ice-cooled solution of 6-amino-1-hexanol (3.52g, 30.0mmol) and triethylamine (4.17ml, 30.0mmol) in DCM (40ml) was added dropwise a solution of 1-adamantanecarbonyl chloride (3.97g, 20.0mmol). The coolant was removed and the resulting suspension was stirred at ambient temperature for 4h. The reaction mixture was washed

sequentially with 10% aqueous citric acid (100ml), aqueous 2M sodium hydroxide (100ml) and brine (100ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate was evaporated at reduced pressure to afford the title compound (3.58g, 64%). ^{1}H NMR 5.59 (1H, br s), 3.63 (2H, t, 6.3), 3.28-3.21 (2H, m), 2.04 (3H, s), 1.85 (6H, br s), 1.77-1.72 (7H, m), 1.57-1.32 (8H, m).

Step b *Toluene-4-sulfonic acid 6-((adamantane-1-carbonyl)-amino)-hexyl ester*. To an ice-cooled solution of the product from step a (3.58g, 12.8mmol), triethylamine (3.13ml, 22.5mmol) and 4-dimethylaminopyridine (catalytic amount) in DCM (25ml) was added, in a single portion, *p*-toluenesulfonyl chloride (4.28g, 22.4mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 3h. The reaction mixture was washed sequentially with 10% aqueous citric acid (30ml), 10% aqueous potassium carbonate (30ml) and brine (30ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate evaporated at reduced pressure to afford the title compound.

Step c *Adamantane-1-carboxylic acid (6-pyrrolidin-1-yl-hexyl)-amide.* To an ice-cooled solution of the product from step b in acetonitrile (25ml) was added pyrrolidine (6.41ml, 76.8mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 20h. The mixture was partitioned between ethyl acetate (100ml) and water (100ml). The aqueous phase was discarded and the organic phase extracted with aqueous 2M hydrochloric acid (100ml). The organic phase was discarded and the aqueous phase was washed with further ethyl acetate (50ml). The pH of the aqueous phase was adjusted to pH 11 and then extracted twice with chloroform (100ml). The combined organic phases were washed with brine (100ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound (4.34g, 100%). ^{1}H NMR 5.54 (1H, br s), 3.26-3.20 (2H, m), 2.50-2.40 (6H, m), 2.05 (3H, s), 1.85-1.73 (14H, m), 1.52-1.50 (4H, m), 1.36-1.33 (4H, m).

Step d *Adamantan-1-yl-methyl-(6-pyrrolidin-1-yl-hexyl)-amine bis-hydrochloride.* To a solution of the product from step c (2.00g, 6.02mmol) in THF (20ml) was added a solution of lithium aluminium hydride (1.0M in THF, 12.0ml, 12.0mmol). The reaction mixture was heated at reflux for 23h and allowed to cool. The reaction mixture was quenched sequentially with water (0.46ml), aqueous 2M sodium hydroxide (0.46ml) and water (1.37ml). Ethyl acetate (30ml) and anhydrous magnesium sulfate added and the suspension filtered through a plug of celite. The

filter-cake was washed sequentially with ethyl acetate (70ml) and chloroform (100ml). The filtrate was evaporated at reduced pressure and the residue treated with hydrogen chloride in 1,4-dioxan (10ml). The solvent was evaporated at reduced pressure and the residue suspended in ether (50ml). The solid was isolated by vacuum filtration and washed with further ether. The solid was dried *in vacuo* to afford the title compound.

Step e *N,N'-Bis(*tert-*butyoxycarbonyl)-N''-(adamantan-1-yl-methyl)-N''-(6-pyrrolidin-1-yl-hexyl)-guanidine*. The title compound was prepared as in Example 50 step a with the product from Example 77 step d replacing N-benzylmethylamine. ^{1}H NMR 9.30 (1H, br s), 3.43 (2H, br s), 3.16 (2H, br s), 2.51-2.40 (6H, m), 1.79 (4H, br s), 1.70-1.49 (34H, m), 1.31-1.30 (4H, m).

Step f *N-Adamantan-1-yl-methyl-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride*. The title compound was prepared as in Example 2 step c with the product from Example 77 step e replacing the product of Example 2 step b. ^{1}H NMR (DMSO-d_6) 11.0 (1H, br s), 7.85 (4H, br s), 3.49-3.42 (2H, m), 3.36-3.28 (2H, m), 3.06-2.89 (6H, m), 1.98-1.83 (7H, m), 1.68-1.47 (16H, m), 1.30-1.23 (4H, m). Microanalysis found C 56.11 H 9.83 N 11.73. $C_{22}H_{42}Cl_2N_4$-$2H_2O$ requires C 56.28 H 9.88 N 11.93.

Example 78

N-(2-Adamantan-1-yl-ethyl)-N-(6-pyrrolidin-1-yl-hexyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 77 with adamantan-1-yl-acetyl chloride replacing adamantylcarbonyl chloride in step a. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 7.43 (4H, br s), 3.45-3.42 (2H, m), 3.28-3.19 (4H, m), 3.07-2.92 (4H, m), 1.95-1.85 (7H, m), 1.68-1.48 (16H, m), 1.29-1.28 (6H, m). Microanalysis found C 52.93 H 10.02 N 10.83. $C_{23}H_{44}Cl_2N_4$-$4H_2O$ requires C 53.17 H 10.09 N 10.78.

Example 79

N-(4-Chlorobenzyl)-N-(8-pyrrolidin-1-yl-octyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,8-dibromooctane replacing 1,5-dibromopentane in step a. ^{1}H NMR (DMSO-d_6) 10.9 (1H, br s), 7.62 (4H, br s), 7.47-7.43 (2H, m), 7.26-7.24 (2H, m), 4.60 (2H, s), 3.46-3.44 (2H, m), 3.28-3.23 (2H, m), 3.04-2.92 (4H, m), 1.95-1.85 (4H, m), 1.64 (2H, br s), 1.48 (2H, br s), 1.23 (8H, br s). Microanalysis found C 51.66 H 8.33 N 11.92. $C_{20}H_{35}Cl_3N_4$-$1.55H_2O$ requires C 51.57 H 8.24 N 12.03.

Example 80

N-(4-Chlorobenzyl)-N-(9-pyrrolidin-1-yl-nonyl)-guanidine bis-hydrochloride

The title compound was prepared as in Example 69 with 1,9-dibromononane replacing 1,5-dibromopentane in step a. ^{1}H NMR (DMSO-d_6) 11.1 (1H, br s), 7.70 (4H, br s), 7.46 (2H, d, 9), 7.27 (2H, d, 9), 4.61 (2H, s), 3.46-3.41 (2H, m), 3.28-3.23 (2H, m), 3.04-2.92 (4H, m), 1.95-1.85 (4H, m), 1.64 (2H, br s), 1.47 (2H, br s), 1.21 (10H, br s). Microanalysis found C 51.79 H 8.48 N 11.37. $C_{21}H_{37}Cl_3N_4$-$2H_2O$ requires C 51.69 H 8.47 N 11.48.

Example 81

N-(2-Pyrrolidin-1-yl-ethyl)-2-naphthalenesulfonamide

To an ice-cooled solution of 2-pyrrolidin-1-yl-ethylamine (1.00g, 8.76mmol) and triethylamine (1.22ml, 8.76mmol) in DCM (20ml) was added portionwise 2-naphthalenesulfonyl chloride (1.98g, 8.73mmol). The coolant was removed and the resultant solution was stirred at ambient temperature for 16h. The organic phase was washed sequentially twice with water (20ml) and brine (20ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to obtain the title compound as a white solid (1.81g, 68%). ^{1}H NMR 8.45 (1H, d, 1.5), 7.99-7.83 (4H, m), 7.66-7.61 (2H, m), 5.80-5.20 (1H, br s), 3.06-3.02 (2H, m), 2.53 (2H, m), 12.36-2.32 (4H, m), 1.74-1.65 (4H, m). Microanalysis found C 62.96 H 6.74 N 9.11. $C_{16}H_{20}N_2O_2S$ requires C 63.13 H 6.62 N 9.20.

Example 82

N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 81 with 3-pyrrolidin-1-yl-propylamine replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.43 (1H, s), 7.99-7.59 (7H, m), 3.11 (2H, t, 5.7), 2.54-2.49 (6H, m), 1.81 (4H, m), 1.68-1.63 (2H, m). Microanalysis found C 63.85 H 7.04 N 8.76. $C_{17}H_{22}N_2O_2S$ requires C 64.12 H 6.96 N 8.80.

Example 83

N-(4-Pyrrolidin-1-yl-butyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 81 with 4-pyrrolidin-1-yl-butylamine replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.41 (1H, s), 7.90 (4H, m), 7.60 (2H, m), 2.96 (2H, t), 2.69 (4H, m), 2.59 (2H, t), 1.92 (4H, m), 1.61 (4H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 57.49, H 6.90, N 7.14. $C_{18}H_{25}ClN_2O_2S$ requires C 57.26, H 6.93, N 7.42.

Example 84

N-(2-Piperidin-1-yl-ethyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 81 with 2-piperidin-1-yl-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.45 (1H, s), 7.93 (3H,m), 7.83 (1H, m), 7.64 (2H, m), 2.99 (2H, t), 2.31 (2H, t), 2.14 (4H, m), 1.44 (6H, m). Found C 63.88, H 7.03, N 8.87. $C_{17}H_{22}N_2O_2S$ requires C 64.12, H 6.96, N 8.79.

Example 85

N-(4-(4-Methyl-piperazin-1-yl)-butyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 81 with 4-(4-methyl-piperazin-1-yl)-butylamine replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.43(1H, s), 7.86 (4H, m), 7.63 (2H, m), 3.00 (2H, t), 2.54 (8H, m), 2.32 (6H, m), 1.54 (4H, m). The bis-hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated to afford the title compound as a white solid. Found C 52.14, H 6.92, N 9.58. $C_{19}H_{29}Cl_2N_3O_2S$ requires C 52.53, H 6.73, N 9.67.

Example 86

N-(2-Pyrrolidin-1-yl-ethyl)-N-methyl-2-naphthalenesulfonamide.

To an ice-cooled solution of 2-naphthalenesulfonyl chloride (2.27g, 10.0mmol) and triethylamine (2.00ml, 14.4mmol) in DCM (30ml) was added methyl-(2-pyrrolidin-1-yl-ethyl)-amine[1](1.28g, 10.0mmol). The coolant was removed and the resultant solution stirred at ambient temperature for 1.5h. The organic phase was washed sequentially twice with water (30ml), then brine (30ml), and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (100:10:1 DCM:methanol:ammonia). The purified material was treated with aqueous hydrochloric acid (1M, 20ml) and the resultant solid was removed by filtration and dried *in vacuo* to obtain the title

compound as a white solid (909mg, 26%). ^{1}H NMR (DMSO-d_6) 10.52 (1H, br s), 8.51 (1H, s), 8.22-8.07 (3H, m), 7.84-7.68 (3H, m), 3.59-3.37 (6H, m), 3.09-3.01 (2H, m), 2.77 (3H, s), 2.01-1.87 (4H, m). Microanalysis found C 57.28 H 6.74 N 7.83. $C_{17}H_{23}ClN_2O_2S$ requires C 57.53 H 6.53 N 7.89.

Example 87

N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfinamide.

Step a *Naphthalene-2-sulfinic acid methyl ester.* To an ice-cooled suspension of 2-naphthalenethiol (2.16g, 18.7mmol) and potassium carbonate (5.68g, 41.1mmol) in methanol (60ml) was added N-bromosuccinimide (7.32g, 41.1mmol). The coolant was removed after 10 minutes and the reaction mixture stirred at ambient temperature for 2h. The reaction mixture was diluted with ethyl acetate (70ml) and washed sequentially with water (100ml), twice with saturated aqueous sodium hydrogen carbonate (70ml) and brine (100ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to afford the title compound (2.34g, 83%). ^{1}H NMR 8.28 (1H, s), 8.01-7.92 (3H, m), 7.72-7.60 (3H, m), 3.51 (3H, s).

Step b *N-(3-Pyrrolidin-1-yl-propyl)-2-naphthalenesulfinamide.* To a cooled (-30^{0}C) solution of 3-pyrrolidin-1-yl-propylamine (641mg, 5.00mmol) in THF (10ml) was added a solution of lithium diisopropylamide (1.5M, 3.30ml, 4.95mmol). The solution was stirred at this temperature for 20 minutes and then added dropwise to a cooled (-78^{0}C) solution of the product of step a (1.03g, 5.00mmol) in THF (10ml). The reaction was stirred at this temperature for 3h and then allowed to warm to ambient temperature and stirred at ambient temperature for 16h. The reaction was quenched with saturated aqueous ammonium chloride (70ml) and then extracted thrice with ethyl acetate (70ml). The combined organic layers were extracted with aqueous hydrochloric acid (1M, 100ml) and the acidic phase washed with ethyl acetate (70ml). The pH of the acidic phase was adjusted (pH11) with ammonia (880) and extracted thrice with DCM (70ml). The combined DCM extracts were washed with brine and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography to obtain the title compound (54mg, 3%). The title compound was converted to the corresponding hydrochloride salt with hydrogen chloride in 1,4-dioxan. ^{1}H NMR (DMSO-d_6) 9.79 (1H, s), 8.43-

8.06 (4H, m), 7.83-7.67 (4H, m), 3.45-3.44 (2H, m), 3.10-3.07 (2H, m), 2.90-2.81 (4H, m), 1.95-1.74 (6H, m). Microanalysis found C 57.43 H 6.75 N 7.73. $C_{17}H_{23}ClN_2OS$-0.5HCl requires C 57.17 H 6.63 N 7.84.

Example 88

1-[4-(Naphthalene-2-sulfony)-butyl]-pyrrolidine

Step a *4-(2-Naphthalenesulfanyl)-butanoic acid ethyl ester.* To a stirred ice-cooled solution of 2-naphthalenethiol (3.20g, 20.0mmol) in DMF (40ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 880mg, 22.0mmol). The suspension was stirred at this temperature for 15 minutes and then treated with a solution of ethyl 4-bromobutyrate (3.15ml, 22.0mmol) in DMF (20ml). The coolant was removed and the reaction mixture was stirred at ambient temperature for 16h. The reaction mixture was partitioned between ethyl acetate (200ml) and water (200ml), and the aqueous phase discarded. The organic phase was washed twice with brine (200ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (5:1 hexane:ethyl acetate) to afford the title compound (4.56%, 83%). ^{1}H NMR 7.78-7.74 (4H, m), 7.48-7.42 (3H, m), 4.15 (2H, q, 7.2), 3.08 (2H, t, 7.2), 2.50 (2H, t, 7.2), 2.07-1.97 (2H, m), 1.25 (3H, t, 7.2).

Step b *4-(2-Naphthalenesulfonyl)-butyric acid methyl ester.* To a solution of the product of step a (1.04g, 3.80mmol) in DCM (10ml) was added in a single portion *meta*-chloroperoxybenzoic acid (3.27g, 11.37mmol). The resultant suspension was stirred at ambient temperature for 30 minutes. The reaction was diluted with DCM (70ml) and washed sequentially with saturated aqueous sodium hydrogen carbonate (100ml) and brine (100ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate) to afford the title compound (1.02g, 88%). ^{1}H NMR 8.50 (1H, s), 8.04-7.86 (4H, m), 7.70-7.42 (2H, m), 4.09 (2H, q, 7.2), 3.30-3.25 (2H, m), 2.46 (2H, t, 7.2), 2.12-2.05 (2H, m), 1.22 (3H, t, 7.2).

Step c *4-(2-Naphthalenesulfonyl)-butan-1-ol.* To a cooled (-78^{0}C) solution of the product of step b (1.00g, 3.27mmol) in THF (10ml) was added dropwise a solution of lithium aluminium hydride (1M, THF, 3.50ml, 3.50mmol) and the mixture was stirred at this temperature for 3h. The reaction mixture was treated sequentially with water

(0.14ml), aqueous sodium hydroxide (2M, 0.14ml) and water (0.42ml) and allowed to warm to ambient temperature. Sodium sulfate was added and the resultant suspension filtered through a pad of celite and the filter-cake washed with further ethyl acetate (150ml). The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (3:1 ethyl acetate:hexane) to afford the title compound (524mg, 61%). ^{1}H NMR 8.50 (1H, s), 8.04-7.86 (4H, m), 7.72-7.63 (2H, m), 3.66-3.62 (2H, m), 3.27-3.21 (2H, m), 1.91-1.83 (2H, m), 1.71-1.65 (2H, m), 1.56 (1H, br s).

Step d *4-(2-Naphthalenesulfonyl)-butyraldehyde.* To a solution of the product of step c (524mg, 1.98mmol) and triethylamine (0.829ml, 5.96mmol) in DMSO (10ml) was added a solution of sulfur trioxide-pyridine (948mg, 5.96mmol) in DMSO (10ml) and the reaction mixture stirred at ambient temperature for 15 minutes. The reaction mixture was poured into ice-water (150ml) and then extracted thrice with ethyl acetate (60ml). The combined organic phases were washed with aqueous citric acid (70ml) and brine (70ml), then dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (2:1 ethyl acetate:hexane) to afford the title compound (457mg, 88%). ^{1}H NMR 9.75 (1H, s), 8.50 (1H, s), 8.05-7.65 (6H, m), 3.26-3.22 (2H, m), 2.71 (2H, t, 6.9), 2.15-2.04 (2H, m).

Step e *1-[4-(Naphthalene-2-sulfony)-butyl]-pyrrolidine.* The title compound was prepared as in Example 17 step d with the product from Example 88 step d replacing the product of Example 17 step c. ^{1}H NMR 8.50 (1H, m), 8.04-7.86 (4H, m), 7.72-7.64 (2H, m), 3.24-3.19 (2H, m), 2.42-2.37 (6H, m), 1.86-1.56 (8H, m). Microanalysis found C 68.22 H 7.45 N 4.38. $C_{18}H_{23}NO_2S$ requires C 68.10 H 7.30 N 4.41.

Example 89

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-2-naphthalenesulfonamide

The title compound was prepared as in Example 81 with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.42 (1H, s), 7.85 (4H, m), 7.62 (2H, m), 3.05 (3H, m), 2.26 (1H, m), 2.25 (3H, s), 2.10 (1H, m), 1.76-1.48 (6H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 57.21, H 6.79, N 7.96. $C_{17}H_{23}Cl\ N_2O_2S$ requires C 57.53, H 6.53, N 7.89.

Example 90

N-(2-(1-Methyl-piperidin-2-yl)-ethyl)-2-naphthalenesulfonamide

Step a *N-(tert-Butoxycarbonyl)-2-piperidin-2-yl-ethanol*. The title compound was prepared as in Example 52 step a with 2-piperidin-2-yl-ethanol replacing 4-chlorobenzylamine. ^{1}H NMR 4.40 (1H, br m), 3.97-3.93 (1H, br m), 3.63-3.56 (1H, br m), 3.36 (1H, br m), 2.72-2.63 (1H, m), 1.98-1.89 (1H, m), 1.75-1.27 (16H, m).

Step b *2-(2-Amino-ethyl)-piperidine-1-carboxylic acid t-butyl ester*. To an ice-cooled solution of the product of step a (5.00g, 21.8mmol) , triphenylphosphine (7.41g, 28.3mmol) and phthalimide (4.16g, 28.3mmol) in THF (50ml) was added dropwise diethylazodicarboxylate (4.45ml, 28.3mmol). The coolant was removed and the reaction stirred at ambient temperature for 16h. The solvent was removed at reduced pressure and the residue was purified by flash column chromatography (2:1 hexane:ethyl acetate). A solution of this material in ethanol (100ml) was treated with hydrazine hydrate (5.30ml) and the resultant reaction mixture was heated at reflux for 1h. The resultant solid was removed by filtration and the filter-cake washed with further ethanol (50ml). The filtrate was evaporated at reduced pressure and the residue was suspended in chloroform (50ml) and the solid residue was removed by filtration. The filtrate was evaporated at reduced pressure to afford the title compound as an oil (2.58g, 52%). ^{1}H NMR 4.36 (1H, br s), 3.95 (1H, bd, 13.5), 2.77-2.60 (3H, m), 1.99-1.93 (1H, m), 1.70-1.38 (18H, m).

Step c *N-(2-(1-(tert-Butoxycarbonyl) piperidin-2-yl)-ethyl)-naphthalenesulfonamide*. The title compound was prepared as in Example 81 with the product from Example 90 step b replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.42 (1H, m), 7.97-7.82 (4H, m), 7.64-7.59 (2H, m), 4.28-4.24 (1H, m), 3.88-3.84 (1H, m), 3.19 (1H, m), 2.60-2.53 (2H, m), 1.91-1.87 (1H, m), 1.64-1.28 (16H, m).

Step d *N-(2-(Piperidin-2-yl)-ethyl)-naphthalenesulfonamide*. To a solution of the product of step c (3.29g, 7.89mmol) in $CHCl_3$ (8ml) was added trifluoroacetic acid (16ml) and the reaction mixture was stirred at ambient temperature for 20h. The excess trifluoroacetic acid was removed at reduced pressure and the residue partitioned between aqueous 10% potassium carbonate (50ml) and $CHCl_3$ (50ml). The $CHCl_3$ layer was removed and the aqueous phase was extracted with further $CHCl_3$ (50ml). The combined organic phases were washed with brine and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure to afford

the title compound (2.42g, 97%). ^{1}H NMR ($CHCl_3$) 8.43 (1H, d, 1 5), 7.98-7.86 (4H, m), 7.76-7.60 (2H, m), 3.20-3.01 (5H, m), 2.60-2.55 (2H, m), 1.60-1.19 (8H, m).

Step e *N-(2-(1-Methyl-piperidin-2-yl)-ethyl)-2-naphthalenesulfonamide.* To a stirred solution of the product of step d (2.42g, 7.63mmol) and aqueous formaldehyde (37%, 3.3ml) in acetonitrile (25ml) was added portionwise sodium cyanoborohydride (788mg, 11.4mmol). The resultant suspension was stirred at ambient temperature for 30 minutes. The pH was adjusted to 6 with acetic acid and the resultant solution stirred at ambient temperature for 30 minutes. The mixture was evaporated at reduced pressure and the residue treated with methanol (50ml) and ammonia solution (880, 50ml). The aqueous phase was extracted twice with DCM (50ml) and the combined organic phases were dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (338mg, 13%) as an oil. The oil was treated with hydrogen chloride in 1,4-dioxan and the solvent removed *in vacuo*. The residue was suspended in diethyl ether and the solid removed by filtration, to obtain the title compound as the hydrochloride salt. ^{1}H NMR (DMSO-d_6) 10.46-10.23 (1H, br s), 8.45-7.64 (8H, m), 3.01 (1H, m), 3.03-2.80 (4H, m), 2.64-2.56 (3H, m), 2.06-1.34 (8H, m). Microanalysis found C 57.43 H 7.08 N 7.27. $C_{18}H_{25}ClN_2O_2S$-$0.5H_2O$ requires C 57.21 H 6.93 N 7.41.

Example 91

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide

Step a *2S-(Methoxy-methyl-carbamoyl)-pyrrolidine-1-carboxylic acid* tert-*butyl ester.* To a solution of N-tert-butoxycarbonyl-L-proline (10.76 g, 50 mmol), N,N-diisopropylethylamine (9.6 ml, 55 mmol), N,O-dimethylhydroxylamine hydrochloride (5.36 g, 55 mmol) and 1-hydroxybenzotriazole (6.75g, 50 mmol) in DCM (150 ml) was added 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDC) (9.5 g, 50 mmol) at 0°C. The solution was stirred at ambient temperature for 16h, washed with water (100 ml), saturated aqueous sodium hydrogen carbonate (100 ml), 1N hydrochloric acid (100 ml), and water again (100 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure to afford the product as a colourless oil (11.1 g, 86%). ^{1}H NMR 4.70 and 4.60 (1H, 2xm), 3.76 and 3.69 (3H, 2xs), 3.60-3.30 (2H, m), 2.10-1.75 (4H, m), 1.43 and 1.39 (9H, 2xs).

Step b *2S-Formyl-pyrrolidine-1-carboxylic acid* tert-*butyl ester.* To a suspension of lithium aluminium hydride (2.12 g, 56.0 mmol) in THF (80 ml) was added dropwise a solution of the product from step a (11.1 g, 43 mmol) in THF (80 ml) at 0°C. The temperature was allowed to rise to ambient temperature and the stirring was continued for 1h. The reaction mixture was cooled to 0°C and 2M aqueous sodium hydroxide (11 ml) was slowly added. The mixture was stirred at ambient temperature for 30 mins, the precipitate was filtered through Celite, and the filtrate was evaporated. The residue was dissolved in ethyl acetate (50 ml) and the solution was successively washed with aqueous 1M hydrochloric acid (30 ml), water (30 ml) and brine (30 ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated to afford the product as a colourless oil (6.3 g, 74%). ^{1}H NMR 9.51 and 9.42 (1H, 2xs), 4.10 and 4.00 (1H, 2xm), 3.45 (2H, m), 1.93 (4H, m), 1.43 and 1.40 (9H, 2xs).

Step c *3-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl)-acrylic acid ethyl ester.* The product of step b (6.3 g, 31.6 mmol) and (carbethoxymethylene)triphenylphosphorane (11.0 g, 31.6 mmol) were refluxed in THF (50 ml) for 2h. The solvent was evaporated and the residue was triturated with hexane:ethyl acetate 1:1 (60 ml). The precipitate was filtered, the filtrate was evaporated. The residue was purified by flash column chromatography (hexane:ethyl acetate 80:20) to afford colourless oil (8.2 g, 97%). ^{1}H NMR 6.80 (1H, bd), 5.80 (1H, d), 4.50 and 4.55 (1H, 2xbr s), 4.15 (2H, m), 3.41 (2H, m), 2.00 (1H, m), 1.77 (3H, m), 1.40 (9H, s), 1.24 (3H, t).

Step d *3-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl)-propionic acid ethyl ester* A round bottom flask containing the product of step c (8.1 g, 30.2 mmol), 10% palladium-on-charcoal (0.80 g) and THF:methanol 1:1 (150 ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred for 2h under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate was evaporated to afford the title compound as a colourless oil (7.3g, 89%). ^{1}H NMR 4.10 (2H, m), 3.79 (1H,br s), 3.29 (2H, m), 2.29 (2H, m), 1.90-1.61 (6H, m), 1.43 (9H, s), 1.23 (3H, t).

Step e *3-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl)-propan-1-ol.* The title compound was prepared as in Example 88 step c with the product from Example 91 step d replacing the product of Example 88 step b. ^{1}H NMR (DMSO-d_6) 4.34 (1H, t), 3.62 (1H, m), 3.38 (2H, m), 3.22 (2H, m), 1.85-1.23 (17H, m).

Step f *3-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl)-propylamine.* The title compound was prepared as in Example 90 step b with the product from Example 91 step e

replacing the product of Example 90 step a. ^{1}H NMR (DMSO-d_6) 3.61 (1H, br s), 3.36 (2H, br s), 3.20 (2H, m), 2.49 (2H, m), 1.82-1.16 (17H, m).

Step g *N-(3-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide* The title compound was prepared as in Example 81 with the product from Example 91 step f replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.44 (1H, s), 7.92 (4H, m), 7.60 (2H, m), 5.70 and 4.50 (1H, 2xbr s), 3.72 (1H, br s), 3.25 (2H, m), 3.04 (2H, m), 1.87- 1.24 (17H, m).

Step h *N-(3-(Pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide* The title compound was prepared as in Example 90 step d with the product from Example 91 step g replacing the product of Example 90 step c. ^{1}H NMR (DMSO-d_6) 8.41(1H, s), 8.11 (2H, m), 8.03 (1H, d), 7.80 (1H, m), 7.67 (2H, m), 6.00 (1H, br s), 2.92-2.75 (5H, m), 1.75 (1H, m), 1.60 (2H, m), 1.39 (4H, m), 1.15 (1H, m).

Step i *N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-naphthalenesulfonamide.* The title compound was prepared as in Example 90 step e with the product from Example 91 step h replacing the product of Example 90 step d. ^{1}H NMR 8.42 (1H, s), 7.86 (4H, m), 7.63 (4H, m), 3.20 (1H, m), 3.06 (1H, m), 2.83 (1H, m), 2.30 (5H, m), 1.83-1.53 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan, the solvent was evaporated and the residue was triturated with diethyl ether. Found C 55.59, H 7.06, N 7.23. $C_{18}H_{25}$ Cl N_2O_2S-1.1 mol of H_2O requires C 55.61, H 7.05, N 7.21.

Example 92

N-(3-(1-Methyl-piperidin-3-yl)-propyl)-2-naphthalenesulfonamide.

Step a *N-(3-Pyridin-3-yl-propyl)-phthalimide.* To a stirred ice-cooled solution of 3-pyridinepropanol (1.29ml, 10.0mmol), triphenylphosphine (3.41g, 13.0mmol) and phthalimide (1.91g, 13.0mmol) in THF (20ml) was added in three portions diethylazodicarboxylate (2.23ml, 13.0mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 20h. The reaction mixture was diluted with ethyl acetate (50ml) and extracted twice with aqueous hydrochloric acid (60ml). The acidic phases were combined and treated with ammonia (880) until pH 11 was achieved and then extracted twice with DCM (100ml). The combined organics were washed with brine (100ml) and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (3:1 ethyl acetate:hexane) to obtain the title compound (2.67g,

100%). ^{1}H NMR 8.47-8.41 (2H, m), 7.86-7.46 (5H, m), 7.26-7.20 (1H, m), 3.77 (2H, t, 7.2), 2.70 (2H, t, 7.8), 2.10-2.00 (2H, m).

Step b *N-(3-(1-Methyl-pyridin-3-yl)-propyl)-phthalimide iodide.* To a solution of the product of step a (1.33g, 5.00mol) in acetone (5ml) was added iodomethane (0.467ml, 7.50mmol) and the resultant solution heated at reflux for 4h. The resultant suspension was filtered and the recovered solid washed with ether (50ml) and the title compound (1.50g, 74%) was dried *in vacuo*. ^{1}H NMR (DMSO-d_6) 8.93 (1H, s), 8.82-8.80 (1H, d, 6), 8.48-8.46 (1H, m), 8.06-8.00 (1H, m), 7.89-7.82 (4H, m), 4.29 (3H, s), 3.65 (2H, t, 6.6), 2.84 (2H, t, 8.1), 2.07-1.93 (2H, m).

Step c *N-(3-(1-Methyl-piperidin-3-yl)-propyl)-phthalimide* To a cooled (-78^{0}C) suspension of the product of step b (1.49g, 3.65mmol) in methanol (36ml) was added portionwise sodium borohydride (270mg, 7.30mmol) and the resultant suspension stirred at this temperature for 20 minutes. The suspension was allowed to warm to 0^{0}C and the reaction stirred for a further 30 minutes. The suspension was treated with aqueous 2M hydrochloric acid (3.6ml) and the stirring was continued for a further 1h. The reaction mixture was treated with sufficient aqueous 2M sodium hydroxide to pH 11 and water (100ml) was added. The aqueous phase was extracted thrice with DCM (100ml) and the combined organic extracts were dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue was dissolved in methanol (10ml) and treated with palladium on charcoal (150mg). The resultant suspension was stirred under a hydrogen atmosphere (*via* balloon) for 16h. The suspension was filtered through a pad of celite and the filter-cake was washed with methanol (100ml). The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (437mg, 42%). ^{1}H NMR 7.87-7.82 (2H, m), 7.74-7.69 (2H, m), 3.72-3.65 (2H, m), 2.89-2.82 (2H, m), 2.28 (3H, s), 1.89-0.84 (11H, m).

Step d *N-(3-(1-Methyl-piperidin-3-yl)-propyl)-2-naphthalenesulfonamide.* To a stirred solution of the product of step c (437mg, 1.53mmol) in ethanol (10ml) was added hydrazine hydrate (0.37ml) and the reaction heated at reflux for 1.5h. The resultant suspension was filtered, the filter-cake was washed with further ethanol (20ml) and the filtrate was evaporated. The residue was suspended in DCM (20ml) and the solid was removed by filtration. The filtrate was evaporated at reduced pressure and the residue was dissolved in DCM (5ml). The solution was treated sequentially, with ice-cooling, with triethylamine (0.290ml, 2.08mmol) and 2-

naphthalenesulfonyl chloride (217mg, 1.39mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 2h. The reaction was diluted with DCM (20ml), washed with water (20ml) and brine (20ml), and dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to afford the title compound (240mg, 45%). ^{1}H NMR 8.44 (1H, d, 1.2), 7.99-7.59 (6H, m), 2.98 (2H, t, 6.9), 2.76-2.69 (2H, m), 2.24 (3H, s), 1.87-1.84 (3H, m), 1.64-1.46 (5H, m), 1.21-1.13 (2H, m), 0.75 (1H, m). Microanalysis found C 64.32 H 7.75 N 7.59. $C_{19}H_{26}N_2O_2S$-0.5H_2O requires C 64.19 H 7.76 N 7.88.

Example 93

N-(3-(1-Methyl-piperidin-4-yl)-propyl)-2-naphthalenesulfonamide.

The title compound was prepared as in Example 92 with 4-pyridinepropanol replacing 3-pyridinepropanol. ^{1}H NMR 8.44 (1H, d, 1.8), 7.99-7.82 (4H, m), 7.66-7.62 (2H, m), 4.46 (1H, br m), 2.98 (2H, t, 6.9), 2.76-2.69 (2H, m), 2.23 (3H, s), 1.85-1.42 (6H, m), 1.21-1.11 (5H, m). Microanalysis found C 66.06 H 7.58 N 8.05. $C_{19}H_{26}N_2O_2S$ requires C 65.86 H 7.56 N 8.09.

Example 94

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-1-naphthalenesulfonamide.

The title compound was prepared as in Example 81 with 1-naphthalenesulfonyl chloride replacing 2-naphthalenesulfonyl chloride and with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. ^{1}H NMR 8.67 (1H, d), 8.25 (1H, m), 8.06 (1H, d), 7.95 (1H, d), 7.57 (3H, m), 3.07 (1H, m), 2.90 (2H, m), 2.27 (4H, m), 2.00(1H, m), 1.81 (1H, m), 1.55 (4H, m), 1.41 (2H, m). Found C 63.73, H 6.95, N 9.01. $C_{17}H_{22}N_2O_2S$ requires C 64.12, H 6.96, N 8.80.

Example 95

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-4-toluenesulfonamide.

The title compound was prepared as in Example 81 with 4-toluenesulfonyl chloride replacing 2-naphthalenesulfonyl chloride and with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. The hydrochloride salt was prepared by treatment with hydrogen chloride in 1,4-dioxan. ^{1}H NMR (DMSO-d_6) 7.62 (2H, d, 8.1), 7.47 (1H, t, 5.1), 7.37 (2H, d, 8.1), 2.86-2.70 (3H, m), 2.37 (3H, s),

2.09 (3H, s), 1.98-1.93 (2H, m), 1.76-1.49 (4H, m)1.29-1.16 (2H, m). Microanalysis found C 52.52 H 7.30 N 8.53. $C_{14}H_{23}ClN_2O_2S$ requires C 52.73 H 7.27 N 8.79

Example 96

N-(2-(1-Methyl-pyrrolidin-2-yl)-ethyl)-4-chlorophenylsulfonamide.

The title compound was prepared as in Example 81 with 4-chlorophenylsulfonyl chloride replacing 2-naphthalenesulfonyl chloride and with 2-(1-methyl-pyrrolidin-2-yl)-ethylamine replacing 2-pyrrolidin-1-yl-ethylamine. The hydrochloride salt was prepared by treatment with hydrogen chloride in 1,4-dioxan. ^{1}H NMR (DMSO-d_6) 8-7 (1H, br s), 7.82-7.77 (2H, m), 7.50-7.46 (2H, m), 3.10-3.01 (3H, m), 2.39 (1H, m), 2.28 (3H, s), 2.15-2.12 (1H, m), 1.82-1.42 (6H, m). Microanalysis found C 51.65 H 6.44 N 8.99. $C_{13}H_{19}ClN_2O_2S$ requires C 51.56 H 6.32 N 9.25.

Example 97

N-(2-(1-Methyl-pyrrolidin-2S-yl)-ethyl)-(4-chlorophenyl)-methanesulfonamide.

Step a *2S-Hydroxymethyl-pyrrolidine-1-carboxylic acid* tert-*butyl ester.* The title compound was prepared as in Example 52 step a with (S)-(+)-pyrrolidinemethanol replacing 4-chlorobenzylamine. ^{1}H NMR 3.94 (1H, m), 3.61 (2H, m), 3.45 (1H, m), 3.30 (1H, m), 2.01 (1H, m), 1.79 (2H, m), 1.58 (1H, m), 1.52 (1H, s), 1.47 (9H, s).

Step b *2S-Tosyloxymethyl-pyrrolidine-1-carboxylic acid* tert-*butyl ester.* To a solution of the product of step a (4.0 g, 20.0 mmol) and triethylamine (3.3 ml, 24.0 mmol) in DCM (100 ml) was added p-toluenesulfonyl chloride (3.8 g, 20.0 mmol) and 4-dimethylaminopyridine (0.2 g) at 0°C. The solution was stirred at ambient temperature for 5h, then it was washed successively with water (50 ml), saturated aqueous sodium hydrogen carbonate (50 ml) and brine (50 ml). The organic phase was dried over anhydrous magnesium sulfate, the solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate 70:30) to afford the title compound (4.3 g, 61 %). ^{1}H NMR 7.77 (2H, d), 7.34 (2H, d), 4.10 (1H, m), 3.90 (2H, m), 3.29 (2H, m), 2.44 (3H, s), 1.92-1.80 (4H, m), 1.37 (9H, s).

Step c *2S-Cyanomethyl-pyrrolidine-1-carboxylic acid* tert-*butyl ester.* The product of step b (4.3 g, 12.1 mmol) and potassium cyanide (1.6 g, 24.2 mmol) were heated together in dimethyl sulfoxide at 110°C for 3h. The reaction mixture was cooled to ambient temperature and poured into water (200 ml). The product was extracted with ethyl acetate (3x50 ml), the combined organic extracts were washed with brine, dried

over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The residue was purified by flash column chromatography (hexane:ethyl acetate 70:30) to afford the the title compound as a colourless oil (1.46 g, 57.5%). ^{1}H NMR 4.00 (1H, br s), 3.41 (2H,m), 2.74 (2H, m), 2.16 (1H, m), 1.92 (3H, m), 1.47 (9H, s).

Step d *2S-(2-Aminoethyl)-pyrrolidine-1-carboxylic acid* tert-*butyl ester.* The product of step c (1.45 g, 6.9 mmol) was suspended in methanol saturated with ammonia (50 ml), Raney-Nickel (*ca.* 1.0 g) and hydrogen hexachloroplatinate (IV) hydrate (80 mg dissolved in 1 ml of water) were added . The mixture was stirred in a Parr bottle under H_2 pressure (about 40 psi) for 24 h. The reaction mixture was filtered through Celite and the filtrate was evaporated. The crude material was purified by flash chromatography (DCM:methanol:amonia (880) 90:10:1) to afford the title compound (1.18g, 80%). ^{1}H NMR 3.90 (1H, m), 3.30 (2H, m), 2.71 (2H, t), 1.87-1.45 (17H, m).

Step e *N-(2-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl-ethyl)-(4-chlorophenyl)-methanesulfonamide.* To a solution the product of step d (0.27g, 1.26mmol) and triethylamine (0.23ml, 1.62mmol) in DCM (15 ml), cooled under an atmosphere of argon to -78°C, was added dropwise a solution of (4-chlorophenyl)-methanesulfonyl chloride[2] (0.34g, 1.5mmol) in DCM (5 ml). The resultant solution was stirred for 18h, allowing to warm to ambient temperature. The solution was washed with water, dried over anhydrous magnesium sulfate and the solvent was evaporated. The material was purified by flash column chromatography (DCM:ethyl acetate 90:10) afforded the product (0.29g, 57%). ^{1}H NMR 7.34 (4H,s), 6.15 (1H, br s), 4.20 (2H, s), 3.96 (1H, m), 3.28 (2H, m), 3.02 (2H, m), 2.80 (1H, m), 1.95-1.45 (6H, m), 1.45 (9H, s).

Step f *N-(2-(1-Methyl-pyrrolidin-2S-yl)-ethyl)-(4-chlorophenyl)-methanesulfonamide.* The product of step e (0.29 g, 0.72 mmol) was dissolved in trifluoroacetic acid (3 ml) and the solution was stirred for 1h. The trifluoroacetic acid was evaporated *in vacuo*, the residue was dissolved in DCM (20 ml) and the organic solution was washed with 10% aqueous potassium carbonate (20ml), dried over anhydrous magnesium sulfate and the solvent was evaporated to afford colourless foam. The foam was dissolved in 1,2-dichloroethane (5 ml) and cooled to 0°C, aqueous formaldehyde (37%, 0.1 ml, 1.4 mmol), followed by sodium triacetoxyborohydride (0.26 g, 1.2 mmol) were added and the mixture was stirred for 2h. Saturated sodium hydrogen carbonate solution was added (20 ml) and the product was extracted with DCM (20ml). The organic phase was dried over anhydrous magnesium sulfate, the solvent was evaporated and the

residue was purified by flash column chromatography (DCM:methanol:ammonia (880) 90:10:1) to afford the title compound (0.15g, 67%). ^{1}H NMR 7.36 (4H, s), 4.19 (2H, s), 3.20 (1H, m), 3.04 (2H, m), 2.50 (1H, m), 2.31 (3H, s), 2.19 (1H, m), 1.86-1.50 (6H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.22, H 6.60, N 8.04. $C_{14}H_{22}Cl_2N_2O_2S$ requires C 47.59, H 6.28, N 7.93.

Example 98

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)-sulfonamide

The title compound was prepared as in Example 91 with 4-chlorophenylsulfonyl chloride replacing 2-naphthalenesulfonyl chloride in step g. ^{1}H NMR 7.79 (2H, d), 7.45 (2H, m), 3.12 (1H, m), 3.00 (1H, m), 2.76 (1H, m), 2.24 (3H, s), 2.20 (2H, m), 1.80-1.37 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.76, H 6.35, N 8.11. $C_{14}H_{22}Cl_2N_2O_2S$ requires C 47.59, H 6.28, N 7.93.

Example 99

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)-methanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f replacing the product of Example 97 step d in step e. ^{1}H NMR 7.36 (4H, s), 4.18 (2H, s), 3.00 (2H, m), 2.87 (1H, m), 2.20 (5H, m), 1.73-1.45 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.64, H 6.67, N 7.28. $C_{15}H_{24}Cl_2N_2O_2S$-0.6 H_2O requires C 47.58, H 6.72, N 7.40.

Example 100

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-phenyl-methanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and phenyl-methanesulfonyl chloride replacing respectively the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ^{1}H NMR 7.40 (5H, m), 4.22 (2H, s), 3.00 (2H, m), 2.87 (1H, m), 2.19 (3H, s), 2.16 (2H, m), 1.71-1.35 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.24, H 7.70, N 8.07. $C_{15}H_{25}ClN_2O_2S$-1.0H_2O requires C 51.31, H 7.76, N 7.98.

Example 101

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-(4-bromophenyl)-methanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and (4-bromophenyl)-methanesulfonyl chloride[2] replacing respectively the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ^{1}H NMR 7.50 (2H, m), 7.27 (2H, m), 4.16 (2H, s), 3.03 (2H, m), 2.88 (1H, m), 2.24 (5H, m), 1.75-1.54 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 43.55, H 5.90, N 6.57. $C_{15}H_{24}BrClN_2O_2S$ requires C 43.75, H 5.87, N 6.80.

Example 102

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-(4-chlorophenyl)-ethanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and 2-(4-chlorophenyl)-ethanesulfonyl chloride[2] replacing respectively the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ^{1}H NMR 7.29 (2H, m), 7.16 (2H, m), 3.21 (2H, m), 3.09 (4H, m), 2.97 (1H, m), 2.32 (3H, s), 2.23 (2H,m), 1.77-1.41 (8H, m). Found C 55.46, H 7.44, N 8.09. $C_{16}H_{25}ClN_2O_2S$ requires C 55.72, H 7.31, N 8.12.

Example 103

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-3-(4-chlorophenyl)-propanesulfonamide

The title compound was prepared as in Example 97 steps e and f, with the product from Example 91 step f and 2-(4-chlorophenyl)-propanesulfonyl chloride[2] replacing respectively the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride in step e. ^{1}H NMR 7.31 (2H, m), 7.16 (2H, d), 3.14 (2H, m), 3.00 (3H, m), 2.78 (2H, t), 2.35 (3H, s), 2.28 (2H, m), 2.15 (2H, m), 1.78-1.47 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.39, H 7.22, N 7.00. $C_{17}H_{28}Cl_2N_2O_2S$ requires C 51.64, H 7.14, N 7.08.

Example 104

N-(4-(1-Methyl-pyrrolidin-2S-yl)-butyl)-(4-chlorophenyl)-methanesulfonamide

The title compound was prepared as in Example 97, steps b-f, with the product from Example 91 step e replacing 2S-hydroxymethyl-pyrrolidine-1-carboxylic acid *tert*-butyl ester as the substrate in step b. ^{1}H NMR 7.36 (4H, m), 4.30 (1H, br s), 4.21 (2H, s), 3.09 (1H, m), 3.00 (2H, t), 2.32 (3H, s), 2.19-1.26 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.20, H 6.93, N 7.31. $C_{16}H_{26}Cl_2N_2O_2S$ requires C 50.39, H 6.87, N 7.35.

Example 105

N-(5-(1-Methyl-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)-methanesulfonamide

Step a *5-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentanoic acid ethyl ester.* A solution of triethyl 4-phosphonocrotonate (3.6ml, 16.3mmol) in THF (20ml) was added dropwise to a slurry of sodium hydride (60% dispersion in mineral oil, 0.72g, 18.0mmol) in THF (20ml) at 0°C under an atmosphere of argon. The mixture was allowed to warm to ambient temperature, stirred for 20 mins, then cooled to -20°C and a solution of the product from Example 91 step b in THF (30 ml) was added dropwise. The mixture was allowed to warm to ambient temperature and stirred for 2h, then it was partitioned between water (100 ml) and ethyl acetate (100 ml). The organic phase was washed with brine, dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure. The crude product was purified by flash column chromatography (hexane:ethyl acetate 80:20). A round bottom flask containing the purified material (1.9 g), 10% palladium-on-charcoal (0.2 g) and THF:methanol 1:1 (30 ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to afford the title compound (1.85 g, 46%). ^{1}H NMR 4.12 (2H, q), 3.73 (1H, br s), 3.3 (2H, m), 2.30 (2H, t), 1.91-1.60 (8H, m),1.46 (9H, s), 1.30 (2H, m), 1.25 (3H, t).

Step b *5-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentan-1-ol.* The title compound was prepared as in Example 88 step c with the product of Example 105 step a replacing the product of Example 88 step b.

Step c *5-(1-(*tert*-Butoxycarbonyl)-pyrrolidin-2S-yl)-pentylamine.* The title compound was prepared as in Example 90 step b with the product of Example 105 step b replacing the product of Example 90 step a.

Step d *N-(5-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)-methanesulfonamide* . The title compound was prepared as in Example 97 step e with the product of Example 105 step c replacing the product of Example 97 step d.

Step e *N-(5-(1-Methyl-pyrrolidin-2S-yl)-pentyl)-(4-chlorophenyl)-methanesulfonamid.e* The title compound was prepared as in Example 97 step f with the product from Example 105 step d replacing the product of Example 97 step e. ^{1}H NMR 7.33 (4H, m), 4.50 (1H, br s), 4.19 (2H, s), 3.06 (1H, m), 2.97 (2H, t), 2.29 (3H, s), 2.14 (1H, m), 1.96 (2H, m), 1.66 (3H, m), 1.45 (3H, m), 1.25 (5H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.26, H 7.20, N 6.89. $C_{17}H_{28}Cl_2N_2O_2S$ requires C 51.64, H 7.14, N 7.09.

Example 106

N-(3-Pyrrolidin-1-yl-propyl)-(4-chlorophenyl)-methanesulfonamide

The title compound was prepared as in Example 97 step e with 3-pyrrolidin-1-yl-propylamine replacing the product of Example 97 step d. ^{1}H NMR 7.36 (4H, s), 4.19 (2H, s), 3.10 (2H, t), 2.60 (2H, t), 2.47 (4H, br s), 1.68 (6H, m). Found C 52.72, H 6.86, N 8.66%; $C_{14}H_{21}ClN_2O_2S$ requires C 53.07, H 6.68, N 8.84%.

Example 107

N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

Step a *N-*tert-*Butoxycarbonyl-N'-(3-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-sulfamide.* To an ice-cooled solution of chlorosulfonyl isocyanate (0.64ml, 7.4mmol) in DCM (15 ml) was added dropwise a solution of dry *tert*-butanol (1.0 ml, 10.8 mmol) in DCM (10 ml). The solution was allowed to warm to ambient temperature, stirred for 10 min and added dropwise to an ice cooled solution of the product from Example 91 step f (1.3 g, 5.7 mmol) and triethylamine (1.2ml, 8.6mmol) in DCM (20ml). The mixture was stirred for 18h, allowed to warm to ambient temperature. The solution was washed with water (20ml), dried over anhydrous magnesium sulfate and the solvent was evaporated. Purification by flash column chromatography (DCM:ethyl acetate 90:10) of the residue afforded the title product (1.67g, 72%). ^{1}H NMR 7.63 (1H, s), 5.50 and 5.30 (1H, 2xbr s), 3.80 (1H, br s), 3.30 (2H, m), 3.09 (2H, br s), 1.92-1.39 (26H, m).

Step b *N-(*tert-*Butoxycarbonyl)-N-(4-Chlorobenzyl)-N'-(3-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-sulfamide.* To an ice-cooled solution of the product of step a (1.6g, 3.93mmol) and 4-chlorobenzyl bromide (0.8g, 3.90mmol) in dry DMF (10 ml) was added sodium hydride (0.17g, 4.3 mmol, 60% dispersion in oil). The mixture was allowed to warm slowly to ambient temperature over 18h. Water (50ml) was added and the mixture was extracted with ethyl acetate (2x30ml). The combined organic extracts were washed with water, dried over anhydrous magnesium sulfate and evaporated. Purification by flash column chromatography (DCM:ethyl acetate 95:5) of the residue afforded the product (1.56g, 75%). ^{1}H NMR 7.30 (4H, m), 5.40 and 5.25 (1H, 2xbr s), 4.80 (2H, s), 3.75 (1H, br s), 3.29 (2H, m), 2.84 (2H, br s), 1.92-1.39 (26H, m).

Step c *N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product from Example 107 step b replacing the product of Example 97 step e. ^{1}H NMR 7.31 (4H, m), 4.50 (1H, br s), 4.18 (2H, s), 3.14 (1H, m), 3.07 (1H, m), 2.89 (1H, m), 2.33 (3H, s), 2.25 (2H, m), 1.79-1.43 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 46.26, H 6.44, N 10.63. $C_{15}H_{25}Cl_2N_3O_2S$. 0.3 mol water requires C 46.46, H 6.65, N 10.84.

Example 108

N-Benzyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

Step a *N-Benzyl-N'-(*tert-*butoxycarbonyl)-sulfamide.* The title compound was prepared as in Example 107 step a with benzylamine replacing the product of Example 91 step f.

Step b *N-Benzyl-N'-(*tert-*butoxycarbonyl)-N'-(3-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-sulfamide.* To an ice-cooled solution of the product from Example 91 step e (0.9g, 3.9mmol) and the product of step a (1.22g, 3.9mmol) and triphenylphosphine (1.33g, 5.07mmol) in THF (10ml) was added a solution of diethyl azodicarboxylate (0.87ml, 5.07mmol) in THF (3ml). The yellow solution was allowed to warm to ambient temperature and stirred for 2h. The solvent was evaporated and the residue was purified by flash chromatography (hexane:ethyl acetate 70:30) to isolate the title compound (1.7g, 88%). ^{1}H NMR 7.33 (5H, m), 5.60 (1H, br s), 4.13 (2H, m), 3.80 (1H, br s), 3.59 (2H, m), 3.30 (2H, m), 1.84-1.44 (26H, m).

Step c *N-Benzyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide*. The title compound was prepared as in Example 97 step f with the product from Example 108 step b replacing the product of Example 97 step e. ^{1}H NMR 7.31 (5H, m), 4.60 (1H, br s), 4.21 (2H, s), 3.23 (1H, m), 3.05 (1H, m), 2.93 (1H, m), 2.40 (3H, s), 2.35 (2H, m), 1.83-1.48 (8H, m). Found C 56.00, H 8.10, N 12.93. $C_{15}H_{25}N_3O_2S$-0.6H_2O requires C 55.90, H 8.20, N 13.04.

Example 109

N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2R-yl)-propyl)-sulfamide

Step a *3-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2R-yl)-propan-1-ol.* The title compound was prepared as in Example 91 steps a-e with N-(*tert*-butoxycarbonyl)-D-proline replacing N-(*tert*-butoxycarbonyl)-L-proline in step a.

Step b *N-(4-Chlorobenzyl)-N'-(*tert-*butoxycarbonyl)-sulfamide.* The title compound was prepared as in Example 107 step a with 4-chlorobenzylamine replacing the product from Example 91 step f.

Step c *N-(4-Chlorobenzyl)-N'-(*tert-*butoxycarbonyl)-N'-(3-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2R-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 108 step b using the products derived from Example 109 steps a and b.

Step d *N-(4-Chlorobenzyl)-N'-(3-(1-methyl-pyrrolidin-2R-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product from Example 108 step c replacing the product of Example 97 step e. ^{1}H NMR 7.34 (4H, m), 4.30 (1H, br s), 4.20 (2H, s), 3.08 (2H, m), 2.93 (1H, m), 2.34 (3H, s), 2.27 (2H, m), 1.78-1.50 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 45.93, H 6.66, N 10.74. $C_{15}H_{25}Cl_2N_3O_2S$-0.53H_2O requires C 45.97, H 6.70, N 10.72.

Example 110

N-Cyclohexyl-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with cyclohexylmethylamine replacing benzylamine in step a. ^{1}H NMR 4.06 (1H, t), 3.07 (2H, m), 2.98 (1H, m), 2.87 (2H, t), 2.32 (3H, s), 2.23 (2H, m), 1.77-1.46 (14H, m), 1.21 (3H, m), 0.95 (2H m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.98, H 9.39, N 11.38; $C_{15}H_{32}ClN_3O_2S$-1.13H_2O requires C 48.13, H 9.23, N 11.22.

Example 111

N-(2-(4-Chlorophenyl)-ethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with 2-(4-chlorophenyl)ethylamine replacing benzylamine in step a. ^{1}H NMR 7.28 (2H, m), 7.16 (2H,d), 4.05 (1H, br s), 3.28 (2H, m), 3.12 (1H, m), 2.96 (1H, m), 2.85 (3H, m), 2.31 (3H, s), 2.21 (2H, m), 1.76-1.40 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 45.29, H 6.98, N 10.10. $C_{16}H_{27}Cl_2N_3O_2S$-1.47H_2O requires C 45.45, H 7.14, N 9.94.

Example 112

N-(4-Chlorophenyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with 4-chloroaniline replacing benzylamine in step a. ^{1}H NMR 7.27 (2H, m), 7.12 (2H, m), 3.08 (2H, m), 2.85 (1H, m), 2.26 (2H, m), 2.24 (3H, s), 1.75-1.47 (8H, m). Found C 47.82, H 6.72, N 12.09. $C_{14}H_{22}ClN_3O_2S$-1.0H_2O requires C 48.01, H 6.92, N 12.00.

Example 113

N-(4-Bromobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

The title compound was prepared as in Example 107 with 4-bromobenzyl bromide replacing 4-chlorobenzyl bromide, in step b. ^{1}H NMR 7.46 (2H, d), 7.23 (2H, d), 4.70 (1H, br s), 4.14 (2H, s), 3.12 (1H, m), 3.02 (1H, m), 2.88 (1H, m), 2.32 (3H, s), 2.24 (2H, m), 1.78-1.40 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 41.91, H 6.17, N 9.59. $C_{15}H_{25}BrClN_3O_2S$ requires C 42.21, H 5.90, N 9.85.

Example 114

N-(4-Iodobenzyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

The title compound was prepared as in Example 107 with 4-iodobenzyl bromide replacing 4-chlorobenzyl bromide, in step b. ^{1}H NMR 7.67 (2H, d), 7.11 (2H, d), 4.50 (1H, br s), 4.15 (2H, s), 3.12 (1H, m), 3.04 (1H, m), 2.90 (1H, m), 2.32 (3H, s), 2.29 (2H, m), 1.78-1.42 (8H, m). Found C 40.77, H 5.79, N 9.41. $C_{15}H_{24}IN_3O_2S$-0.35H_2O requires C 40.61, H 5.61, N 9.47.

Example 115

N-(4-Chlorobenzyl)-N'-(2-(1-methyl-pyrrolidin-2S-yl)-ethyl)-sulfamide

The title compound was prepared as in Example 107, with the product from Example 97 step d replacing the product of Example 91 step f in step a. ^{1}H NMR 7.31 (4H, m), 4.60 (1H, br s), 4.18 (2H, s), 3.20 (1H, m), 3.05 (2H, m), 2.41 (1H, m), 2.32 (3H, s), 2.18 (1H, m), 1.86-1.58 (6H, m). Found C 50.46, H 6.75, N 12.42. $C_{14}H_{22}ClN_3O_2S$ requires C 50.67, H 6.68, N 12.66.

Example 116

N-(4-Chlorobenzyl)-N'-(4-(1-methyl-pyrrolidin-2S-yl)-butyl)-sulfamide

Step a *2S-(4-Amino-butyl)-pyrrolidine-1-carboxylic acid* tert-*butyl ester.* The title compound was prepared as in Example 97 steps b-d with the product of Example 91 step e replacing the product of Example 97 step a. ^{1}H NMR 3.70 (1H, m), 3.30 (2H, m), 2.70 (2H, t), 1.86- 1.21 (21H, m).

Step b *N*-tert-*Butoxycarbonyl-N'-(4-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-butyl)-sulfamide.* The title compound was prepared as in Example 107 step a with the product from step a replacing the product of Example 91 step f. ^{1}H NMR 7.50 (1H, br s), 5.17 and 4.50 (1H, 2xbr s), 3.75 (1H, br s), 3.30 (2H, m), 3.08 (2H, m), 1.88-1.31 (28H, m).

Step c *N-(*tert-*Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(4-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-butyl)-sulfamide.* The title compound was prepared as Example 107 step b with the product from step b replacing the product of Example 107 step a. ^{1}H NMR 7.32 (4H, m), 5.23 (1H, t), 4.80 (2H, s), 3.78 (1H, br s), 3.31 (2H, m), 2.80 (2H, m), 1.82-1.49 (6H, m), 1.49 (9H, s), 1.46 (9H, s), 1.25 (4H, m).

Step d *N-(4-Chlorobenzyl)-N'-(4-(1-methyl-pyrrolidin-2S-yl)-butyl)-sulfamide*. The title compound was prepared as in Example 97 step f with the product of step c replacing the product of Example 97 step e. ^{1}H NMR 7.33 (4H, m), 4.60 (1H, br s), 4.30 (1H, br s), 4.20 (2H, s), 3.22 (1H, m), 3.03 (2H, t), 2.41 (3H, s), 2.29-1.33 (12H, m). The hydrochloride salt was prepared in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 48.11, H 6.92, N 10.29. $C_{16}H_{27}Cl_2N_3O_2S$ requires C 48.48, H 6.87, N 10.60.

Example 117

N-(4-Chlorobenzyl)-N'-(5-(1-methyl-pyrrolidin-2S-yl)-pentyl)-sulfamide

Step a *N-(4-Chlorobenzyl)-N'-*(tert-*butoxycarbonyl)-N'-(5-(1-*(tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-pentyl)-sulfamide.* The title compound was prepared as in Example 108 step b using the products derived from Example 105 step b and Example 109 step b. ^{1}H NMR 7.33 (2H, m), 7.26 (2H, m), 5.63 (1H, t), 4.12 (2H, d), 3.72 (1H, m), 3.57 (2H, m), 3.30 (2H, m), 1.91-1.24 (30H, m).

Step b *N-(4-Chlorobenzyl)-N'-(5-(1-methyl-pyrrolidin-2S-yl)-pentyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product of step a replacing the product of Example 97 step e. ^{1}H NMR 7.32 (4H, m), 4.60 (1H, br s), 4.19 (3H, s), 3.05 (1H, m), 3.00 (2H, m), 2.31 (3H, s), 2.16-1.23 (14H, m). Found C 54.33, H 7.61, N 11.04. $C_{17}H_{28}ClN_3O_2S$ requires C 54.60, H 7.55, N 11.24.

Example 118

N-(4-Chlorobenzyl)-N'-(3-(1-(3-(4-chlorophenyl)propyl)-pyrrolidin-2S-yl)-propyl)-sulfamide

The title compound was prepared as in Example 108 with 4-chlorobenzylamine replacing benzylamine in step a, and 3-(4-chlorophenyl)propan-1-al replacing aqueous formaldehyde in step c. ^{1}H NMR 7.30 (6H, m), 7.20 (2H, d), 4.43 (1H, br s), 4.16 (2H, br s), 3.18 (1H, m), 3.02 (1H, m), 2.89 (1H, m), 2.75-2.50 (3H, m), 2.30 (1H, m), 2.11 (2H, m), 1.87-1.36 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 51.46, H 6.39, N 7.76. $C_{23}H_{32}Cl_3N_3O_2S$-0.9H_2O requires C 51.46, H 6.34, N 7.83%.

Example 119

*N-(4-Chlorobenzyl)-N'-(3-(1-(*iso-*butyl)-pyrrolidin-2S-yl)-propyl)-sulfamide*

The title compound was prepared as in Example 108 with 4-chlorobenzylamine replacing benzylamine in step a, and *iso*-butyraldehyde replacing aqueous formaldehyde in step c. ^{1}H NMR 7.31 (4H, m), 5.60 (1H, br s), 4.54 (1H, br s), 4.17 (2H, br s), 3.16 (1H, m), 3.03 (1H, m), 2.93 (1H, m), 2.42-1.48 (13H, m), 0.91 (6H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.59, H 7.39, N 9.81. $C_{18}H_{31}Cl_2N_3O_2S$ requires C 50.94, H 7.36, N 9.90.

Example 120

N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide.

Step a *N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(1-tert-butoxycarbonyl-pyrrolidin-2S-yl)-propyl)-sulfamide.* To a solution of of N-(4-chlorobenzyl)-N'-(3-(pyrrolidin-2S-yl)-propyl)sulfamide (1.03g, 2.87mmol) in 1,4-dioxan (10ml) was added di-*tert*-butyldicarbonate (625mg, 2.87mmol) and the reaction mixture was stirred at ambient temperature for 18h. The solvent was evaporated at reduced pressure and the residue dissolved in chloroform (50ml) and washed sequentially with water (50ml), aqueous citric acid (10%, 50ml) and brine (50ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (2:1 hexane:ethyl acetate). The product was dissolved in DMF (8ml) and cooled in ice. The solution was treated sequentially with iodomethane (0.253ml, 4.06mmol) and sodium hydride (60% dispersion in mineral oil, 185mg, 4.63mmol). The suspension was allowed to warm to ambient temperature over 18h and then water (75ml) was added. The aqueous phase was extracted with ethyl acetate (75ml) and the organic phase was subsequently washed twice with brine (75ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure. The residue was purified by flash column chromatography (3:2 hexane:ethyl acetate) to obtain the title compound (686mg, 52%). ^{1}H NMR 7.35-7.27 (4H, m), 4.27 (2H, s), 3.77 (1H, m), 3.34-3.21 (4H, m), 2.83 (3H, s), 2.65 (3H, s), 1.94-1.24 (17H, m).

Step b *N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 90 step d with the product from Example 120 step a replacing the product of Example 90 step c. ^{1}H NMR 7.35-7.17 (4H, m), 4.27 (2H, s), 3.24-3.18 (2H, m), 3.01-2.95 (2H, m), 2.89-2.86 (1H, m), 2.83 (3H, s), 2.66 (3H, s), 1.78-1.24 (9H, m).

Step c *N-(4-Chlorobenzyl)-N,N'-dimethyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 90 step e with the product from Example 120 step b replacing the product of Example 90 step d. The oil was treated with hydrogen chloride in 1,4-dioxan and the solvent removed *in vacuo*. ^{1}H NMR (free base) 7.35-7.27 (4H, m), 4.28 (2H, s), 3.21 (2H, t, 7.2), 3.10-3.04 (1H, m), 2.83 (3H, s), 2.63 (3H, s), 2.31 (3H, s), 2.20-1.30 (10H, m). Microanalysis found C 49.41 H 7.60 N 10.18. $C_{17}H_{29}ClN_3O_2S$ requires C 49.75 H 7.37 N 10.24.

Example 121

N-(4-Chlorobenzyl)-N-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

Step a *N-(4-Chlorobenzyl)- N'-(*tert-*butoxycarbonyl)- N'-(3-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 108 step b using the products derived from Example 91 step e and Example 109 step b as substrates.

Step b *N-(4-Chlorobenzyl)-N-methyl- N'-(*tert-*butoxycarbonyl)- N'-(3-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-propyl)-sulfamide.* To a solution of the product of step a (1.0g, 1.9mmol) in DMF (5ml) was added sodium hydride (90mg, 2.26mmol; 60% dispersion in mineral oil) at 0°C. The temperature was allowed to warm to ambient temperature and the stirring was continued for 1h. Iodomethane (0.13ml, 2.1mmol) was added and the stirring was continued overnight. Water (50ml) was added and the product was extracted with ethyl acetate (2x30ml), the organic phase was dried, the solvent was evaporated. Flash column chromatography (hexane:ethyl acetate 70:30) afforded the title compound (0.94g, 91%). ^{1}H NMR 7.28 (4H, m), 4.39 (2H, s), 3.70 (3H, m), 3.30 (2H, m), 2.75 (3H, s), 1.85-1.26 (26H, m).

Step c *N-(4-Chlorobenzyl)-N-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide* The title compound was prepared as in Example 97 step f with the product from Example 121 step b replacing the product of Example 97 step e. ^{1}H NMR 7.31 (4H, m), 4.26 (2H, s), 3.11 (2H, m), 2.95 (1H, m), 2.67 (3H, s), 2.33 (3H, s), 2.22 (2H, m), 1.78-1.44 (8H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

Example 122

N-(4-Chlorobenzyl)-N'-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide

Step a *N-(*tert-*Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-methyl-N'(3-(1-(*tert-*butoxycarbonyl)pyrrolidin-2S-yl)propyl)-sulfamide.* The title compound was prepared as in Example 121 step b with the product from Example 107 step b replacing the product of Example 121 step a. ^{1}H NMR 7.31 (4H, m), 4.82 (2H, s), 3.80 (1H, br s), 3.30 (2H, m), 3.13 (2H, m), 2.79 (3H, s), 1.87-1.26 (26H, m).

Step b *N-(4-Chlorobenzyl)-N'-methyl-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product from Example 122 step a replacing the product of Example 97 step e. ^{1}H NMR 7.32

(4H, m), 4.50 (1H, m), 4.16 (1H, br s), 3 07 (3H, m), 2.79 (3H, s), 2.30 (3H, s), 1.76-1.29 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

Example 123

N-(4-Chlorobenzyl)-N'-(methoxycarbonylmethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide.

Step a *N-(*tert*-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(methoxycarbonylmethyl)-N'(3-(1-(*tert*-butoxycarbonyl)pyrrolidin-2S-yl)propyl)-sulfamide.* The title compound was prepared as in Example 122 step a with methyl bromoacetate replacing iodomethane. ^{1}H NMR 7.31 (4H, m), 4.82 (2H, s), 4.05 (2H, s), 3.70 (4H, br s), 3.27 (4H, m), 1.87-1.26 (26H, m).

Step b *N-(4-Chlorobenzyl)-N'-(methoxycarbonylmethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide.*

The title compound was prepared as in Example 97 step f with the product from Example 123 step a replacing the product of Example 97 step e. ^{1}H NMR 7.31 (4H, m), 5.05 (1H, br s), 4.30 (2H, s), 4.08 (2H, s), 3.75 (3H, s), 3.24 (2H, m), 3.09 (1H, m), 2.30 (3H, s), 2.177-1.22 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

Microanalysis found 45.81 H 6.61 N 8.90 $C_{18}H_{29}Cl_2N_3O_4S$-0.97H_2O requires C 45.82 H 6.61 N 8.90.

Example 124

N-(4-Chlorobenzyl)-N'-(2-hydroxyethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide. The title compound was prepared as in Example 88 step c with the product from Example 123 step b replacing the product of Example 88 step b. ^{1}H NMR 7.29 (4H, m), 4.17 (2H, s), 3.67 (3H, m), 3.35 (2H, m), 3.20 (2H, m), 3.02 (1H, m), 2.27 (3H, s), 2.16-1.20 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

Example 125

N-(4-Chlorobenzyl)-N'-(3-phthalimido-propyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide. To an ice-cooled stirred solution of the product from Example 107 step b (532mg, 1.00mmol) in DMF (5ml) was added portionwise sodium hydride

(60% dispersion in mineral oil, 0.058g, 1.84mmol). The coolant was removed the reaction mixture was stirred at ambient temperature for 1h. N-(3-Bromopropyl)phthalimide (295mg, 1.10mmol) added and the reaction mixture was heated at 100°C for 2h and then allowed to cool. The reaction mixtire was diluted with water (30ml) and extracted twice with ethyl acetate (30ml) and the aqueous phase was discarded. The organic phase was washed thrice with water (30ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue was treated with trifluoroacetic acid (5ml) and the resultant solution stirred at ambient temperature for 1h. The excess trifluoroacetic acid was evaporated at reduced pressure and the residue was dissolved in DCM (30ml). The organic phase was washed with aqueous potassium carbonate (10%, 30ml) and dried over anhydrous magnesium sulfate. The filtrate was dissolved in 1,2-dichloroethane (5ml) and treated sequentially with aqueous formaldehyde (37%, 0.20ml) and sodium triacetoxyborohydride (300mg, 1.42mmol). The resultant suspension was stirred at ambient temperature for 1h and then was quenched with saturated sodium hydrogen carbonate (30ml) and extracted with DCM (30ml). The organic phase was dried over anhydrous magnesium sulfate and the solvent evaporated at reduced pressure. The residue was purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (80mg, 16%). ^{1}H NMR 7.83 (2H, m), 7.71 (2H, m), 7.30 (4H, m), 4.75 (1H, br s), 4.15 (2H, s), 3.71 (2H, m), 3.25 (2H, m), 3.16 (2H, m), 3.02 (1H, m), 2.26 (3H, s), 2.10-1.10 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 54.50 H 6.11 N 9.56 $C_{26}H_{34}Cl_2N_4O_4S$ requires C 54.83 H 6.02 N 9.84.

Example 126

N-(4-Chlorobenzyl)-N'-(3-amino-propyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide. To a stirred solution of the product of Example 125 (200mg, 0.38mmol) in ethanol (2ml) was added hydrazine hydrate (0.06ml) and the reaction mixture was heated at reflux for 1h. The solvent was removed at reduced pressure, the residue was suspended in chloroform (10ml) and the solid removed by filtration. The filtrate was evaporated at reduced pressure and the residue evaporated thrice form chloroform (10ml) to afford the title compound (125mg, 82%). ^{1}H NMR 7.28 (5H, m), 4.12 (2H, s), 3.24 (2H, m), 3.2-2.5 (2H, vbr s), 3.15 (2H, m), 3.03 (1H, m), 2.72 (2H, m), 2.27

(3H, s), 2.14-1.00 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.

Example 127

N-(4-Chlorobenzyl)-N'-(methylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide

Step a. *N-(*tert*-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(carboxymethyl)-N'(3-(1-(*tert*-butoxycarbonyl)pyrrolidin-2S-yl)propyl)-sulfamide.* To a solution of the product of Example 123 step a (3.54g, 5.86mmol) in THF (10ml) was added an aqueous solution of lithium hydroxide (1M, 10ml) and the resultant reaction mixture was stirred at ambient temperature for 18h. The solvent was evaporated at reduced pressure to half the initial volume and diluted with aqueous hydrochloric acid (2M, 5ml) and water (50ml). The aqueous phase was extracted twice with ethyl acetate (50ml) and the combined organic layers were washed with brine (50ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure to afford the title compound. ^{1}H NMR (DMSO-d_6) 13.0 (1H, br s), 7.41(2H, d, 8.4), 7.30 (2H, d, 8.4), 4.75 (2H, s), 4.03 (2H, s), 3.75 (1H, m), 3.18 (4H, m), 2.00-1.10 (22H, m).

Step b *N-(*tert*-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(methylamidomethyl)-N'(3-(1-(*tert*-butoxycarbonyl)pyrrolidin-2S-yl)propyl)-sulfamide.* To an ice-cooled solution of the product from Example 127 step a (590mg, 1.00mmol) in DCM (20ml) was added N-hydroxysuccinimide (126mg, 1.10mmol). The coolant was removed and the reaction stirred at ambient temperature, and then treated with dicyclohexylcarbodiimide (233mg, 1.11mmol), and stirred at this temperature for 1h. The suspension was filtered to remove the solid and methylamine was bubbled through the filtrate for 5 minutes. The reaction mixture was stirred at ambient temperature for a further 1h and then diluted with DCM (20ml). The reaction mixture washed sequentially with saturated aqueous sodium hydrogen carbonate (20ml), water (20ml), aqueous hydrochloric acid(1M, 20ml) and water (20ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate evaporated at reduced pressure to afford the title compound (650mg, q). ^{1}H NMR 7.31 (4H, m), 6.70 (1H, br s), 4.84 (2H, s), 3.91 (2H, s), 3.70 (1H, m), 3.30-3.17 (4H, m), 2.81 (3H, d, 4.5), 1.47 (18H, s), 1.90-1.18 (10H, m).

Step c *N-(4-Chlorobenzyl)-N'-(methylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product from Example 127 step b replacing the product of Example 97 step e. ^{1}H NMR 7.30 (4H, m), 6.50(1H, m), 4.69 (1H, s), 4.23 (2H, s), 3.85 (2H, s), 3.17 (2H, m), 3.03 (1H, m), 2.80 (3H, 5.8), 2.28 (3H, s), 2.17-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 46.63 H 7.04 N 11.93 $C_{18}H_{30}Cl_2N_4O_3S$-$0.5H_2O$ requires C 46.75 H 6.76 N 12.11.

Example 128

N-(4-Chlorobenzyl)-N'-(dimethylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide

The title compound was prepared as in Example 127 with dimethylamine replacing methylamine in step b. ^{1}H NMR 7.29 (4H, m), 6.25(1H, m), 4.30 (2H, d, 5.4), 4.14 (2H, s), 3.24 (2H, m), 3.04 (1H, m), 2.96 (3H, s), 2.93 (3H, s), 2.28 (3H, s), 2.15-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 48.48 H 7.18 N 11.67 $C_{19}H_{32}Cl_2N_4O_3S$ requires C 48.81 H 6.90 N 11.98.

Example 129

N-(4-Chlorobenzyl)-N'-(4-chlorobenzylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide

Step a *N-(*tert*-Butoxycarbonyl)-N-(4-chlorobenzyl)-N'-(4-chlorobenzylamidomethyl)-N'(3-(1-(*tert*-butoxycarbonyl)pyrrolidin-2S-yl)propyl)-sulfamide.* To an ice-cooled solution of the product of Example 127 step a (590mg, 1.00mmol), 4-chlorobenzylamine (0.133ml, 1.10mmol), N-hydroxybenzotriazole hydrate (168mg, 1.10mmol) and 4-dimethylaminopyridine (20mg, 0.16mmol) in DCM (20ml) was added EDC (211mg , 1.10mmol). The coolant was removed and the reaction mixture stirred at ambient temperature for 16h. The reaction mixture was washed sequentially with saturated aqueous sodium hydrogen carbonate (20ml), water (20ml), aqueous hydrochloric acid (1M, 20ml) and water (20ml). The organic phase was dried over anhydrous magnesium sulfate and the filtrate was evaporated at reduced pressure to afford the title compound (675mg, 95%). ^{1}H NMR 7.30 (9H, m), 4.83 (2H, s), 4.42

(2H, d, 6), 3.98 (2H, s), 3.60 (1H, m), 3.50-3.00 (4H, m), 1.45 (9H, s), 1.42 (9H, s), 2.0-1.0 (8H, m).

Step b *N-(4-Chlorobenzyl)-N'-(4-chlorobenzylamidomethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product from Example 129 step a replacing the product of Example 97 step e. ^{1}H NMR 7.32-7.16 (9H, m), 6.81 (1H, m), 4.36 (2H, d, 6), 4.19 (2H, s), 3.84 (2H, s), 3.15 (2H, m), 3.00 (1H, m), 2.24 (3H, s), 2.13-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 51.22 H 6.10 N 10.04 $C_{24}H_{33}Cl_3N_4O_3S$ requires C 51.11 H 6.10 N 9.93.

Example 130

N-(4-Chlorobenzyl)-N'-(benzyloxycarbonylmethyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide

The title compound was prepared as in Example 122 with benzyl bromoacetate replacing iodomethane in step a. ^{1}H NMR 7.39-7.25 (9H, m), 5.18 (2H, s), 4.26 (2H ,d, 6), 4.11 (2H, s), 3.27 (2H, m), 3.08 (1H, m), 2.31 (3H, s), 2.18-1.00 (10H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 47.70 H 6.99 N 6.74 $C_{24}H_{33}Cl_2N_3O_4S$-$4H_2O$ requires C 47.84 H 6.86 N 6.97.

Example 131

N-(4-Chlorobenzyl)-N'-(3-(4-chlorophenyl)propyl)-N'-(3-(1-methyl-pyrrolidin-2S-yl)propyl)-sulfamide. To an ice-cooled stirred solution of the product of Example 107 step b (532mg, 1.00mmol) in DMF (5ml) was added portionwise sodium hydride (60% dispersion in mineral oil, 0.058g, 1.84mmol). The coolant was removed and methanesulfonic acid 3-(4-chlorophenyl)-propyl ester (261mg, 1.10mmol)was added. The reaction mixture was heated at 100^{0}C for 3h and then allowed to cool. The reaction mixture was diluted with water (30ml) and extracted with ethyl acetate (30ml). The organic phase was washed thrice with water (30ml) and dried over anhydrous magnesium sulfate. The filtrate was evaporated at reduced pressure and the residue purified by flash column chromatography (5:4:1 Hexane:DCM:ethyl acetate). The purified material was treated with trifluoroacetic acid (2ml) and the resultant solution stirred at ambient temperature for 1h. The excess trifluoroacetic acid was

evaporated at reduced pressure and the residue dissolved in DCM (30ml). The organic phase was washed with aqueous potassium carbonate (10%, 30ml) and dried over anhydrous magnesium sulfate. The filtrate was dissolved in 1,2-dichloroethane (3ml) and treated sequentially with aqueous formaldehyde (37%, 0.06ml) and sodium triacetoxyborohydride (160mg, 0.75mmol). The resultant suspension was stirred at ambient temperature for 1h, quenched with saturated sodium hydrogen carbonate (30ml) and extracted with DCM (30ml). The organic phase was dried over anhydrous magnesium sulfate and the residue purified by flash column chromatography (90:10:1 DCM:methanol:ammonia) to obtain the title compound (80mg, 16%). ^{1}H NMR 7.32-7.08 (8H, m), 4.62 (1H, br s), 4.12 (2H, s), 3.12 (4H, m), 3.04 (1H, m), 2.59 (2H, m), 2.15 (3H, s), 2.20-1.20 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Microanalysis found C 53.62 H 6.41 N 7.55 $C_{24}H_{34}Cl_3N_3O_2S$ requires C 53.88 H 6.41 N 7.85.

Example 132

N-(4-Chlorobenzyl)-N'-(3-(4R-hydroxy-1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

Step a *2S-(Methoxy-methyl-carbamoyl)- 4R-hydroxy-pyrrolidine-1-carboxylic acid* tert-*butyl ester*. The title compound was prepared as in Example 91 step a with N-(*tert*-butoxycarbonyl)-L-*trans*-4-hydroxyproline replacing with N-(*tert*-butoxycarbonyl)-L-proline. ^{1}H NMR (DMSO-d_6) 5.01 (1H, d), 4.64 (1H, m), 4.22 (1H, br s), 3.71 and 3.68 (3H, 2xs), 3.30 (2H, m), 3.10 and 3.08 (3H, 2xs), 2.20 (1H, m), 1.78 (1H, m), 1.37 and 1.31 (9H, 2xs).

Step b *2S-Formyl-4R-hydroxy-pyrrolidine-1-carboxylic acid* tert-*butyl ester*. The title compound was prepared as in Example 91 step b with the product from Example 132 step a replacing the product of Example 91 step a. ^{1}H NMR 9.45 and 9.44 (1H, 2xbr s), 4.49 (1H, br s), 4.13 and 4.11 91H, 2xm), 3.58 (2H, m), 2.16-1.97 (3H, m), 1.48 and 1.44 (9H, 2xs).

Step c *3-(1-(*tert-*Butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-acrylic acid ethyl ester*. The title compound was prepared as in Example 91 step c with the the product from Example 132 step b replacing the product of Example 91 step b. ^{1}H NMR (DMSO-d_6) 6.80 (1H, dd), 5.86 (1H, d), 4.50 (1H, br s), 4.30 (1H, m), 4.16 (2H, m), 3.53 (2H, m), 2.17 (1H, m), 1.87 (2H, m), 1.43 (9H, s), 1.26 (3H, t).

Step d *3-(1-(*tert-*Butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propionic acid ethyl ester*. The title compound was prepared as in Example 91 step d with the the product

from Example 132 step c replacing the product of Example 91 step c. ^{1}H NMR 4.40 (1H, m), 4.11 (2H ,m), 3.97 (1H, m), 3.94 (2H, m), 2.28 (2H, t), 2.07 (2H, m), 1.78 (3H, m), 1.47 (9H, s), 1.25 (3H, t).

Step e *3-(1-(*tert-*Butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propan-1-ol.* The title compound was prepared as in Example 88 step c with the the product from Example 132 step d replacing the product of Example 88 step b. ^{1}H NMR (DMSO-d_6) 4.80 (1H, d), 4.35 (1H, t), 4.15 (1H, m), 3.72 (1H, m), 3.35 (2H, m), 3.23 (2H, m), 1.90-1.50 (4H, m), 1.38 (9H, s), 1.16 (2H, m).

Step f *N-(4-Chlorobenzyl)-N'-(*tert-*butoxycarbonyl)-N'-(3-(1-(*tert-*butoxycarbonyl)-4R-hydroxy-pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 108 step b using the products derived from Example 109 step b and Example 132 step e. ^{1}H NMR (DMSO-d_6) 8.26 (1H, s), 7.33 (4H, m), 4.81 (1H, d), 4.06 (3H, m), 3.68 (1H, m), 3.30 (2H, m), 1.90-1.22 (24H, m).

Step g *N-(4-Chlorobenzyl)-N'-(3-(4R-hydroxy-1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product from Example 132 step f replacing the product of Example 97 step e. The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan.^{1}H NMR (DMSO-d_6) 10.60 (1H, br s), 7.39 (5H, m), 6.98 (1H, t), 5.50 (1H, br s), 4.33 (1H, br s), 4.01 (2H, d), 3.72 (1H, m), 3.45 (1H, m), 3.30 (1H, m), 2.83 (5H, m), 2.07-1.45 (6H, m).

Example 133

N-(4-Chlorobenzyl)-N'-(3-(4R-(4-chlorobenzyloxy)-1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide

Step a *3-(1-(*tert-*Butoxycarbonyl)-4R-(4-chlorobenzyloxy)-pyrrolidin-2S-yl)-propionic acid ethyl ester.* To a solution of the product from Example 132 step d (0.90g, 3.13mmol) in DMF (10 ml) was added sodium hydride (0.15g, 3.76mmol, 60% dispersion in mineral oil) at 0°C. The temperature was allowed to warm to ambient temperature and the mixture was stirred for 1h, 4-chlorobenzyl bromide was added and the stirring was continued for 16h. The reaction was quenched with water (40ml) and the product was extracted with ethyl acetate (2x20ml), the organic extracts were dried over anhydrous magnesium sulfate, the solvent was evaporated. Purification by flash column chromatography (hexane:ethyl acetate 70:30) afforded the product as a colourless oil (0.36g, 28%). ^{1}H NMR 7.30 (4H, m), 4.50 (2H, m),

4.11 (3H, m), 3.96 (1H, m), 3.70 and 3.50 (1H, 2xbr s), 3.67 (1H, br s), 2.28 (2H, m), 2.12 (2H, m), 1.76 (2H, m), 1.47 and 1.45 (9H, 2xs),1.25 (3H, t).

Step b *3-(1-(*tert-*Butoxycarbonyl)-4R-(4-chlorobenzyloxy)-pyrrolidin-2S-yl)-propan-1-ol.* The title compound was prepared as in Example 88 step c with the product from Example 133 step a replacing the product of Example 88 step b. ^{1}H NMR 7.30 (4H, m), 4.46 (2H, br s), 4.10 (1H, m), 3.96 (1H, br s), 3.67 (3H, m), 3.39 (1H, m),2.13 (1H, m), 1.82 (5H, m), 1.42 (11H, m).

Step c *N-(4-Chlorobenzyl)-N'-(*tert-*butoxycarbonyl)-N'-(3-(1-(*tert-*butoxycarbonyl)-4R-(4-chlorobenzyloxy)-pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 108 step b using the products derived from Example 109 step b and Example 133 step b. ^{1}H NMR 7.30 (8H, m), 5.70 (1H, br s), 4.45 (2H, br s), 4.12 (2H, d), 4.06 (1H, m), 3.96 (1H, br s), 3.60 (2H, m), 3.30 (1H, m), 1.90-1.22 (24H, m).

Step d *N-(4-Chlorobenzyl)-N'-(3-(4R-(4-Chlorobenzyloxy)-1-methyl-pyrrolidin-2S-yl)-propyl)-sulfamide.* The title compound was prepared as in Example 97 step f with the product from Example 133 step c replacing the product of Example 97 step e. ^{1}H NMR 7.30 (8H, m), 4.63 (1H, br s), 4.43 (2H, m), 4.18 (2H, d), 4.11 (1H, m), 3.52 (1H, m), 3.04 (1H, m), 3.04 (1H, m), 2.92 (1H, m), 2.63 (1H, m), 2.43 (1H, m), 2.41 (3H, s), 2.20 (1H, br s),1.97 (1H, m), 1.77 (1H, m), 1.55 (3H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.08, H 5.81, N 8.03. $C_{22}H_{30}Cl_3N_3O_3S$-0.2H_2O requires C 50.13, H 5.83, N 7.97.

Example 134

N-(4-Chlorobenzyl)-N'-(2-pyrrolidin-1-yl-ethyl)-sulfamide. To an ice-cooled solution of of the product from Example 109 step b (321mg, 1.00mmol), 1-(2-hydroxyethyl)pyrrolidine (0.152ml, 1.30mmol) and triphenylphosphine (393mg, 1.50mmol) in THF (2ml) was added in a single portion diethylazodicarboxylate (0.257ml, 1.50mmol). The coolant was removed and the reaction mixture was stirred at ambient temperature for 2h. The reaction mixture was diluted with ethyl acetate (25ml) and washed sequentially with water (20ml), twice with aqueous hydrochloric acid (2M, 25ml) and brine (25ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was dissolved in 1,4-dioxan (5ml) and treated with aqueous hydrochloric acid (2M, 5ml).

The resultant mixture was heated at reflux for 1h and then diluted with further aqueous hydrochloric acid (30ml). The aqueous was washed twice with diethyl ether (30ml) and then the pH was adjusted to 11 with ammonia (880). The now basic phase was extracted twice with chloroform (50ml) and then dried over anhydrous sodium sulfate. The filtrate was evaporated at reduced pressure and the residue was purified by flash column chromatography (200:10:1 DCM:methanol:ammonia) to afford the title compound as a white solid (95mg, 30%). ^{1}H NMR 7.35-7.28 (4H, m), 6.0-4.5 (2H, br s), 4.20 (2H, s), 3.19 (2H, t, 5.7), 2.59 (2H, t, 5.7), 2.50-2.46 (4H, m), 1.73-1.67 (4H, m). Microanalysis found C 49.05 H 6.36 N 13.09 $C_{13}H_{20}ClN_3O_2S$ requires C 49.13 H 6.34 N 13.22.

Example 135

N-(4-Chlorobenzyl)-N'-(3-pyrrolidin-1-yl-propyl)-sulfamide. A solution of 4-chlorobenzylamine (0.610ml, 5.00mmol), 1-(3-aminopropyl)pyrrolidine (0.632ml, 5.00mmol) and sulfamide (480mg, 4.99mol) was heated at reflux for 2h. The reaction was allowed to cool and partitioned between ethyl acetate (20ml) and water (20ml). The aqueous was discarded and the organic phase washed with water (20ml) and brine (20ml). The organic phase was dried over anhydrous sodium sulfate and the filtrate was evaporated at reduced pressure. The residue was purified by flash column chromatography (100:10:1 DCM:methanol) to obtain the title compound as a white solid (365mg, 22%). ^{1}H NMR 7.35-7.28 (4H, m), 4.18 (2H, s), 3.15 (2H, t, 6), 2.61 (2H, t, 6), 2.51 (4H, br m), 1.82-1.67 (6H, m). Microanalysis found C 49.97 H 6.73 N12.50 $C_{14}H_{22}ClN_3O_2S$-0.26H_2O requires C 49.96 H 6.74 N 12.49.

Example 136

N-(4-Chlorobenzyl)-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide

Step a N-*(4-Chlorobenzyl)-methanesulfonamide*. A solution of 4-chlorobenzylamine (12.20g, 86.2mmol) and triethylamine (14.4ml, 103.5mmol) in DCM (200ml) was cooled in an ice bath. Mesyl chloride (7.34ml, 94.9mmol) was added dropwise and the solution was stirred for 10min. The cold bath was removed and the solution stirred for a further 2h. The reaction was diluted with a equal volume of DCM and washed with 10% citric acid solution and brine. The solvent was evaporated and the residue recrystallised from hot ethyl acetate. The product was thus obtained as a colourless crystalline solid (15.34g, 81%).

Step b *N-(*tert-*Butoxycarbonyl)-N-(4-chlorobenzyl)-methanesulfonamide.* To a solution of N-(4-chlorobenzyl)-methanesulfonamide (15.30g, 69.6mmol) and di-*tert*-butyl-dicarbonate (18.27g, 83.6mmol) in DCM (150ml) was carefully added *N,N*-dimethylaminopyridine (848mg, 6.96mmol); there was immediate and vigorous effervescence. The solution was stirred for 30min, by which time effervescence had ceased. The solution was diluted to a total volume of 500ml with DCM and washed twice with 10% citric acid solution and then brine. The solvent was evaporated to give a yellow solid, which was recrystallised from hot propan-2-ol (100ml). The precipitate was collected by filtration and dried *in vacuo* at 50°C to afford the product as a colourless crystalline solid (19.70g, 89%).

Step c *3-(1-(*tert-*Butoxycarbonyl)-pyrrolidin-2S-yl)-propan-1-al.* A solution of oxalyl chloride (1.2ml, 13.7mmol) in DCM (40ml) was cooled to -78°C and dimethylsulfoxide (1.9ml, 27.3mmol) was added dropwise with concomitant effervescence. The solution was stirred for 5 mins, by which time effervescence had ceased, and a solution of the product from Example 91 step e (2.6g, 11.4mmol) in DCM (30ml) was added. The solution was stirred for 20 mins, triethylamine (5.7ml, 41.0mmol) was added, the cold bath was removed and the resultant solution was stirred for 3h. The solution was washed with water (2x50ml), the organic phase was dried over anhydrous magnesium sulfate and the solvent was evaporated under reduced pressure . The crude product was purified by flash column chromatography (hexane:ethyl acetate 70:30) to afford the aldehyde as an oil (2.16 g, 83%). ^{1}H NMR 9.77 (1H, t), 3.83 (1H, m), 3.30 (2H, m), 2.46 (2H, m), 1.99-1.26 (15H, m).

Step d *N-(4-Chlorobenzyl)-4-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-but-1-enesulfonamide.* A solution of the product from step c (0.8g, 3.0mmol) in THF (10 ml) was cooled to -78°C, 1.0M potassium *tert*-butoxide (5.0ml, 5.0mmol) was added dropwise and the solution was stirred for 1h. A solution of the aldehyde from step c of this example (0.57g, 2.5mmol) in THF (10ml) was added and the solution was stirred overnight allowing the temperature to slowly warm to ambient temperature. The reaction mixture was quenched with saturated ammonium chloride solution (30ml) and extracted with diethyl ether (2x15ml). The combined extracts were washed with brine, dried over anhydrous magnesium sulfate, filtered and the solvent was evaporated. Purification by flash column chromatography (hexane:ethyl acetate 1:1) of the residue gave the titled product (0.65g, 62%). ^{1}H NMR 7.30 (4H, m), 6.75 (1H, m),

6.20 (1H, d), 4.74 (1H, m), 4.17 (2H, d), 3.77 (1H, m), 3.30 (2H, m), 2.20 (2H, m), 1.95-1.46 (15H, m).

Step f *N-(4-Chlorobenzyl)-4-(1-(*tert-*butoxycarbonyl)-pyrrolidin-2S-yl)-butane sulfonamide.* A round bottom flask containing the product of step e (0.27g, 0.63mmol), 10% palladium-on-charcoal (30mg) and THF:methanol 1:1 (10ml) was evacuated and flushed with hydrogen three times. The mixture was vigorously stirred overnight under an atmosphere of hydrogen. The catalyst was removed by filtration and the filtrate evaporated to afford the product as a colourless foam (0.21g, 78%). ^{1}H NMR 7.32 (4H, m), 5.10 and 4.90 (1H, 2xbr s), 4.27 (2H d), 3.75 (1H, m), 3.30 (2H, m), 2.90 (2H ,m), 1.80-1.26 (19H, m).

Step g *N-(4-Chlorobenzyl)-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide.* The title compound was prepared as in Example 97 step f with the product from Example 136 step f replacing the product of Example 97 step e. ^{1}H NMR 7.30 (4H, m), 5.00 (1H br s), 4.27 (2H, d), 3.05 (1H, m), 2.92 (2H, m), 2.29 (3H, s), 2.16-1.22 (12H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 47.36, H 6.91, N 6.92. $C_{16}H_{26}Cl_2N_2O_2S$-1.3H_2O requires C 47.56, H 7.11, N 6.93%.

Example 137

N-Cyclohexyl-methyl-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide. The title compound was prepared as in Example 136, with cyclohexyl-methylamine replacing 4-chlorobenzylamine in step a. ^{1}H NMR 4.30 (1H, t), 3.10-2.91 (4H, m), 2.31 (3H, s), 2.16 (1H, m), 2.01-1.67 (13H, m), 1.45 (4H, m), 1.24 (4H, m), 0.94 (2H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.75, H 9.80, N 7.52. $C_{16}H_{33}ClN_2O_2S$-1.5H_2O requires C 50.55, H 9.55, N 7.37%.

Example 138

N-Adamantan-1-yl-methyl-4-(1-methyl-pyrrolidin-2S-yl)-butanesulfonamide. The title compound was prepared according to the procedure of Example 136, with adamantan-1-yl-methylamine replacing 4-chlorobenzylamine in step a. ^{1}H NMR 4.28 (1H, t), 3.03 (3H, m), 2.74 (2H, d), 2.29 (3H, s), 2.12 (1H, m), 1.08-1.23 (26H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and

lyophilised from water and 1,4-dioxan. Found C 55.52, H 9.43, N 6.60. $C_{20}H_{37}ClN_2O_2S$-1.5H_2O requires C 55.62, H 9.33, N 6.49 %.

Example 139

N-(4-Chlorobenzyl)-N'-(4-pyrrolidin-1-yl-butyl)-sulfamide.

Step a. *N-(4-Chlorobenzyl)-N'-*(tert-*butoxycarbonyl)-N'-(1-pent-4-enyl)-sulfamide and N-(4-chlorobenzyl)-N'-*(tert-*butoxycarbonyl)-N,N'-bis(1-pent-4-enyl)-sulfamide* To a solution of the product of Example 109 step b (1.60g, 5.00mmol), 4-penten-1-ol (0.80ml, 7.50mmol) and triphenylphosphine (2.00g, 7.50mmol) in THF was added diethylazodicarboxylate (1.30ml, 7.50mmol). The solution was kept at ambient temperature for 16h. The solvent was evaporated and the two products were separated by flash column chromatography (90:10 hexane:ethyl acetate) to obtain N-(4-chlorobenzyl)-N'-(*tert*-butoxycarbonyl)-N'-(1-pent-4-enyl)-sulfamide (low R_f, 773mg, 40%) and N-(4-chlorobenzyl)-N'-(*tert*-butoxycarbonyl)-N,N'-bis(1-pent-4-enyl)-sulfamide (high R_f, 1.03g, 45%).

Step b. *N-(4-Chlorobenzyl)-N'-*(tert-*butoxycarbonyl)-N'-(1-butan-4-al)-sulfamide.* The title compound was prepared according to the procedure of Example 17, step c using the low R_f material from step a above as substrate.

Step c. *N-(4-Chlorobenzyl)-N'-(*tert-*butoxycarbonyl)-N'-(4-pyrrolidin-1-yl-butyl)-sulfamide.* The title compound was prepared according to the procedure of Example 17, step d with the product of step b above replacing the product of Example 17 step c.

Step d. *N-(4-Chlorobenzyl)-N'-(4-pyrrolidin-1-yl-butyl)-sulfamide.* To a solution of the product of step c above (490mg, 1.10mmol) in dioxan (5ml) was added hydrogen chloride in dioxan (1ml, 4.00mmol) and the solution was stirred at ambient temperature for 16h. The solvent was evaporated and the residue was dissolved in DCM (20ml). The organic phase was washed with 10% aqueous potassium carbonate (2x20ml), dried over anhydrous magnesium sulfate and the solvent was evaporated to afford the title compound (270mg, 71%). ^{1}H NMR 7.31 (4H, m), 4.30 (1H, br s), 4.17 (2H, s), 2.98 (2H, t), 2.56 (4H, m), 2.49 (2H, t), 1.84 (4H, m), 1.63 (4H, m). Found C 52.03, H 7.04, N 11.82. $C_{15}H_{24}ClN_3O_2S$ requires C 52.09, H 6.99, N 12.15%.

Example 140

N-(4-Chlorobenzyl)-N,N'-bis(4-pyrrolidin-1-yl-butyl)-sulfamide.

The high R_f product of Example 139 step a was converted to the title compound according to the procedure of Example 139, steps b-d. ^{1}H NMR 7.30 (4H, m), 4.32 (2H, s), 3.10 (2H, t), 2.95 (2H, m), 2.48 (10H, m), 2.38 (2H, t), 1.80 (8H, m), 1.63 (6H, m), 1.41 (2H, m). The bis-hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 48.42, H 7.80, N 9.94. $C_{23}H_{41}Cl_3N_4O_2S$-1.4 mol H_2O requires C 48.53, H 7.76, N 9.84%.

Example 141

N-(4-Chlorobenzyl)-N'-(5-pyrrolidin-1-yl-pentyl)-sulfamide.

The title compound was prepared according to the procedure of Example 139, using 5-hexen-1-ol in step a instead of 4-penten-1-ol. ^{1}H NMR 7.31 (4H, m), 4.80 (1H, br s), 4.17 (2H, s), 3.00 (2H, t), 2.55 (4H, m), 2.47 (2H, t), 1.80 (4H, m), 1.52 (4H, m), 1.36 (2H, m). Found C 52.14, H 7.46, N 11.49. $C_{16}H_{26}ClN_3O_2S$-0.5 mol H_2O requires C 52.17, H 7.37, N 11.41%.

Example 142

N-(3-(1-Methyl-pyrrolidin-2S-yl)-propyl)-2-cyclohexyl-ethanesulfonamide.

The title compound was prepared according to the procedure of Example 97,steps e and f, with the modification that the product of Example 91 step f and 2-cyclohexyl-ethanesulfonyl chloride was used in step e instead of the product of Example 97 step d and (4-chlorophenyl)-methanesulfonyl chloride. ^{1}H NMR 3.11 (2H, m), 2.98 (3H, m), 2.32 (3H, s), 2.21 (2H, m), 1.86-0.90 (21H, m). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised from water and 1,4-dioxan. Found C 50.78, H 9.67, N 7.45. $C_{16}H_{33}ClN_2O_2S$-1.4 mol H_2O requires C 50.86, H 9.54, N 7.41%.

Example 143

*N-(3-(1-*iso*-Butyl-pyrrolidin-2S-yl)-propyl)-(4-chlorophenyl)-methanesulfonamide.*

The title compound was prepared according to the procedure of Example 97,steps e and f, with the product of Example 91 step f replacing the product of Example 97 step d in step e and *iso*-butyraldehyde replaced aqueos formaldehyde in step f. ^{1}H NMR 7.34 (4H, m), 6.00 (1H, br s), 4.18 (2H, s), 3.11 (1H, m), 2.98 (1H, m), 2.88 (1H, m), 2.35 (2H, m), 2.00 (1H, m), 1.95 (1H, m), 1.78-1.48 (9H, m), 0.90 (6H, t). The hydrochloride salt was prepared with hydrogen chloride in 1,4-dioxan and lyophilised

from water and 1,4-dioxan. Found C 52.49, H 7.67, N 6.75. $C_{18}H_{30}Cl_2N_2O_2S$ requires C 58.81, H 7.39, N 6.84%.

References.

1. J. Med. Chem 1994, 314.
2. WO 97/29092

Histamine H_3 functional assay - guinea pig ileum

The biological activity of the compounds of the examples was measured using the ileal longitudinal muscle, myenteric plexus assay described by Paton and Aboo Zar (*J. Physiol.* 1968, **194**, 13-33). Male Dunkin-Hartley guinea pigs (250-300g) were employed. Briefly, a 50cm portion of ileum proximal to the caecum was removed, after discarding the terminal 20cm. Ileal segments (3cm) were cleaned by passing Krebs-Henseleit buffer containing 3μM mepyramine gently through the ileum using a Pasteur pipette (size: 13.8cm length, 0.65cm diameter). To avoid unnecessary damage to the tissue, Krebs-Henseleit buffer was passed through the ileal segment, while it was lying horizontally on a petri dish. Therefore, the ileum was not over-distended and the buffer flowed through with ease. Each segment was then passed over a Pasteur pipette and the longitudinal muscle layer and adhering myenteric plexus was teased away using moist cotton wool, by stroking tangentially away from the mesenteric attachment. The tissues were suspended in 20ml organ baths containing Krebs-Henseleit buffer at 37±1°C and gassed with 95%CO_2/5%O_2. The tissues were ligated to two parallel stainless steel wires, situated between two platinum electrodes (0.76cm length, 0.06cm diameter). All measurements were recorded isometrically (Grass FTO3 transducer). Following an initial loading tension of 1g, the tissues were stimulated with electrical pulses at a frequency of 0.1Hz and a pulse duration of 0.5msec, as described by Kosterlitz & Watt (*Br. J. Pharmacol.* 1968, 266-276). Initially, the tissues were stimulated at supramaximal (1.3 fold times maximal) voltage for a period of 30 min and then the tissues were washed and re-stimulated. A "sighter dose" of the selective histamine H_3-receptor agonist, R-(α)-methylhistamine (0.3μM) (Arrang *et al. Nature*, 1987, 117-123), was administered. Upon generation of response, the "sighter dose" was removed from the tissues by "washout" (6 washes over 60 min) and during this period the electrical stimulation was switched off. The tissues were then re-stimulated and allowed to stabilise prior to the addition of drug treatments, which were allocated on a randomised block basis to the

organ baths. Following the incubation period, a single cumulative E/[A] curve was obtained. The experimental E/[A] curve data was expressed as the percentage inhibition of the peak height of electrically-stimulated contraction. Antagonist affinity values were calculated from the degree of rightward shift of the R-(α)-methylhistamine E/[A] curves using Schild's methods (Arunlakshana & Schild *Br. J. Pharmacol.* 1959, 48-58). Typical variance in this assay is ± 0.15 log units.

The compounds of the invention were also tested in a guinea pig cortex binding assay, as follows:

Histamine H_3 radioligand binding assay - guinea pig cortex

Preparation of membranes

Male Dunkin Hartley guinea pigs (200-300g) were used. The whole brain was removed and immediately placed in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C). The cortex was dissected, weighed and homogenised in ice-cold 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) (50ml/guinea-pig cortex) using a polytron (Kinematica AG; PT-DA 3020/2TS, 3 x 3s). The homogenate was centrifuged at 100 x g for 5min and the supernatants pooled and stored at 4°C. The pellets were rehomogenised in fresh ice-cold buffer (80ml) and recentrifuged (100 x g for 5min). The supernatants were pooled and pellets rehomogenised and recentrifuged (100 x g for 5min). All supernatants were pooled and centrifuged at 39,800 x g for 12 min at 4°C. The final pellet was resuspended in 20mM Hepes-NaOH buffer (pH7.4 at 21±3°C) to a tissue concentration of 7.5mg.ml^{-1},using a teflon-in-glass homogeniser.

Incubation conditions

Guinea pig cortex membranes (400µl) were incubated for 165 min at 21±3°C in a final volume of 500µl with 20mM Hepes-NaOH buffer containing [^{3}H]-R-α-methylhistamine (50µl; 1nM) and competing compound. Total and non-specific binding of [^{3}H]-R-α-methylhistamine were defined using 50µl of buffer and 50µl of 10µM thioperamide, respectively. The assay was terminated by rapid filtration through Whatman GF/B filters, presoaked (2hr) in 0.1% polyethyleneimine, using a Brandell Cell Harvester. The filters were washed (3 x 3ml) with ice-cold 50mM Tris-HCl (pH6.9 at 21±3°C),

transferred into scintillation vials, 5ml liquid scintillation cocktail was added and after 4 hours the bound radioactivity was determined by counting (4 min) in a Beckman liquid scintillation counter.

Data analysis

Data are analysed using GraphPad prism and the general equation for a competition curve with variable Hill slope (n_H).

$$Y = \text{Non-specific binding} + \frac{\text{(Total binding - Non-specific binding)}}{1+10^{((\log IC_{50}-X).n_H)}}$$

where

X is the log concentration of competing compound,

Y is the binding obtained at each concentration of X,

pIC_{50} is the concentration of the competitor required to compete for half of the specific binding.

The IC_{50} is converted to the K_I using the Cheng Prusoff equation,

$$K_I = IC_{50}/(1+(L/K_D))$$

where

IC_{50} is the concentration of competitor required to compete for half the specific binding,

L is the radioligand concentration used,

K_D is the equilibrium dissociation constant for the radioligand determined by saturation experiments.

The results obtained from the functional and binding assays described above are set out in the Table below:

Table

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
1	7.2	5.4
2	7.3	6.4

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
3	7.1	6.1
4	7.1	6.5
5	7.0	6.1
6	7.3	6.4
7	7.4	6.4
8	7.7	6.2
9	8.3	6.5
10	7.6	6.5
11	7.4	6.3
12	6.2	6.3
13	7.7	6.3
14	7.6	6.0
15	6.1	NT
16	6.2	5.4
17	8.3	7.3
18	8.3	7.3
19	7.3	6.0
20	9.0	6.7
21	7.3	6.8
22	7.1	6.7
23	6.5	5.5
24	8.2	6.2
25	8.1	7.1
26	7.4	6.8
27	6.8	NT
28	7.5	6.7
29	8.4	7.7
30	8.5	7.9
31	8.4	8.0
32	8.5	8.0
33	7.1	6.7

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
34	6.5	6.5
35	8.1	7.7
36	7.3	7.2
37	7.9	7.6
38	7.5	7.2
39	7.4	NT
40	8.4	7.4
41	8.9	7.5
42	7.6	6.4
43	7.0	6.7
44	8.8	7.6
45	8.4	7.5
46	8.5	7.7
47	8.4	7.3
48	8.5	7.6
49	8.2	7.5
50	7.8	6.5
51	8.1	7.0
52	6.5	6.5
53	8.1	7.1
54	7.3	7.1
55	7.5	6.6
56	7.7	7.2
57	7.7	NT
58	8.5	6.7
59	8.0	7.0
60	8.0	8.1
61	8.1	7.8
62	7.5	7.4
63	7.7	7.4
64	7.2	6.2

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
65	8.3	7.1
66	8.6	7.4
67	8.6	7.3
68	8.1	7.3
69	9.0	7.9
70	8.3	8.4
71	8.7	8.4
72	8.3	8.5
73	8.8	7.8
74	8.1	7.9
75	7.6	6.9
76	8.8	8.1
77	8.2	8.0
78	7.1	7.5
79		8.1
80		8.0
81	6.9	5.9
82	6.5	6.0
83	6.6	6.2
84	6.3	6.1
85	6.8	NT
86	5.6	NT
87	5.9	NT
88	6.2	5.9
89	7.0	6.2
90	5.9	NT
91	6.9	6.3
92	5.7	NT
93	5.5	NT
94	5.6	NT
95	5.8	NT

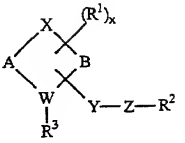
Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
96	5.8	NT
97	5.8	5.5
98	6.1	6.1
99	6.7	6.5
100	6.7	6.3
101	6.6	6.0
102	7.2	6.5
103	6.9	6.5
104	6.4	6.4
105	6.4	6.3
106	6.0	6.2
107	7.0	6.8
108	5.8	NT
109	6.7	NT
110	6.3	5.6
111	5.8	NT
112	6.4	5.8
113	7.0	6.7
114	6.5	7.0
115	6.3	6.4
116	6.9	6.7
117	7.1	NT
118	5.8	NT
119	7.8	5.7
120	6.3	6.3
121	6.5	6.0
122	6.9	6.5
123	6.6	5.5
124	5.9	NT
125	6.5	<5.5
126	6.0	5.5

Example	pK_i (Guinea pig cortex)	pK_b (Guinea pig ileum)
127	5.7	5.7
128	5.5	NT
129	6.1	NT
130	5.3	NT
131	6.0	<5.5
132	6.9	5.8
133	5.6	<5.5
134	6.0	NT
135	6.5	6.2
136	6.5	6.5
137	5.6	NT
138	5.9	NT
139	6.7	6.3
140	8.1	6.5
141	6.6	6.3
142	6.2	5.7
143	6.1	5.5

NT= not tested

CLAIMS

1. A compound of the formula



wherein

A is $(CH_2)_m$, m being from 1 to 3;

B is $(CH_2)_n$, n being from 1 to 3;

x is from 0 to 2;

R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

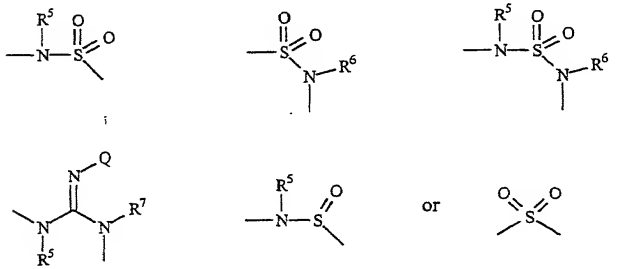
R^3 is absent when -Y-Z-R^2 is attached to W, or is H or C_1 to C_7 hydrocarbyl when -Y-Z-R^2 is not attached to W;

W is nitrogen;

X is $-CH_2-$, -O- or $-NR^4-$, R^4 being H or C_1 to C_3 alkyl;

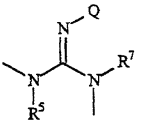
Y replaces a hydrogen atom on any of A, B, W and X, and is C_2 to C_{10} alkylene, in which one non-terminal carbon atom may be replaced by O; and

Z is



wherein R^5, R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O or N, and up to 3 hydrogen

atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R^5 or R^7 to form a five-membered ring or Q is linked to R^2 to form a six-membered ring, provided that when Z is



at least one of R^5 and R^7 is aryl(C_1 to C_3)alkyl or cycloalkyl(C_1 to C_3)alkyl, optionally substituted by halo;

or a pharmaceutically acceptable salt thereof.

2. A compound according to claim 1 wherein R^2 is selected from alkyl, aryl, arylalkyl, cycloalkyl and cycloalkylalkyl, wherein alkyl moieties are optionally substituted by halo, and aryl groups are optionally substituted by C_1 to C_4 alkyl, C_1 to C_4 alkoxy or halo.

3. A compound according to claim 1 wherein R^2 is selected from phenyl, halophenyl, benzyl, halobenzyl, phenylethyl, halophenylethyl, phenylpropyl, halophenylpropyl, phenylbutyl, halophenylbutyl, tolyl, methoxybenzyl, trifluoromethylbenzyl, halo-methoxybenzyl, phenylbenzyl, adamantanemethyl, adamantaneethyl, adamantanepropyl, cyclohexanemethyl, cyclohexaneethyl, and naphthyl.

4. A compound according to any of claims 1 to 3 wherein x is 0.

5. A compound according to any of claims 1 to 3 wherein x is 1 or 2, and R^1 is selected from hydroxy, C_1 to C_9 alkoxy (optionally substituted by halo), C_1 to C_9 cycloalkylalkoxy (wherein the cycloalkyl group is optionally substituted by C_1 to C_4 alkyl or halo, and the alkoxy group is optionally substituted by halo), arylalkoxy (wherein the aryl group is optionally substituted by C_1 to C_4 alkyl, C_1 to C_3 alkoxy or halo, and the alkoxy group is optionally substituted by halo) and C_1 to C_9 alkylamino wherein the alkyl group is optionally substituted by halo.

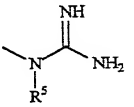
6. A compound according to any preceding claim wherein R^3 is H, C_1 to C_7 alkyl or benzyl

7. A compound according to any preceding claim wherein R^5, R^6 and R^7 are independently selected from H, aryl(C_1 to C_3)alkyl and cycloalkyl(C_1 to C_3)alkyl, and are optionally substituted by halo.

8. A compound according to any preceding claim wherein Y is propylene, butylene, pentylene, hexylene, heptylene, octylene or nonylene.

9. A compound according to any preceding claim wherein $m+n \geq 3$.

10. A compound according to claim 8, wherein $m+n \geq 3$, $Z\text{-}R^2$ is



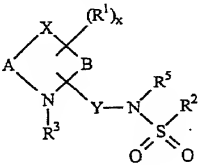
and R^5 is benzyl or halobenzyl.

11. A compound according to any preceding claim, for use in therapy.

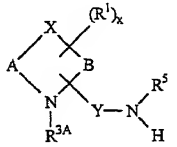
12. A compound which is degraded *in vivo* to yield a compound according to any of claims 1 to 10.

13. A pharmaceutical composition comprising a therapeutically effective amount of a compound according to any of claims 1 to 10, and a physiologically acceptable diluent or carrier.

14. A method of making a compound of the formula

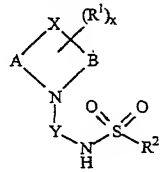


wherein A, B, x, R^1, R^2, R^3, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula R^2SO_2Cl with a compound of the formula

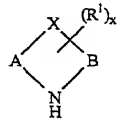


wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group.

15. A method of making a compound of the formula

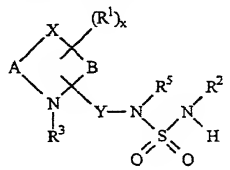


wherein A, B, x, R^1, R^2, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

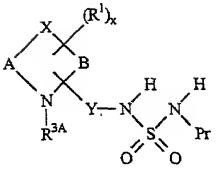


with a compound of the formula Cl-Y-NH-SO_2-R^2.

16. A method of making a compound of the formula

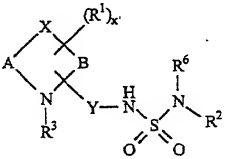


wherein A, B, x, R^1, R^2, R^3, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

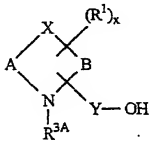


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group and Pr is a protecting group) with a compound of the formula R^2Br, and reacting the product with R^5Br when R^5 is not hydrogen.

17. A method of making a compound of the formula

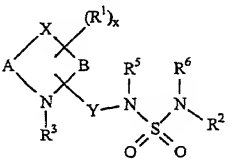


wherein A, B, x, R^1, R^2, R^3, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

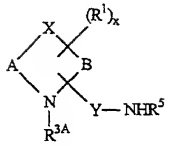


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula R^2-NH-SO_2-NH-Pr, wherein Pr is a protecting group, and reacting the product with R^6Br when R^6 is not hydrogen.

18. A method of making a compound of the formula

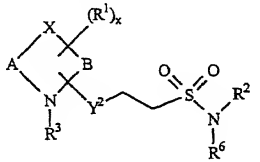


wherein A, B, x, R^1, R^2, R^3, R^5, R^6, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

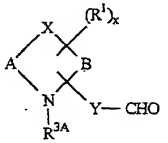


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula R^2R^6NH and sulfamide.

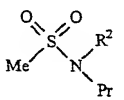
19. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, R^3, R^6 and X are as recited in claim 1 and Y^2 is a bond or C_1 to C_8 alkylene, said method comprising the step of reacting a compound of the formula

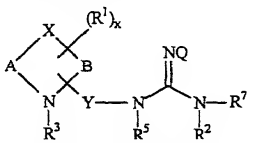


(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula

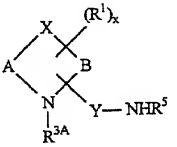


wherein Pr is a protecting group, reducing the reaction product, and (when R^6 is not hydrogen) reacting the reduced product with R^6Br.

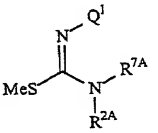
20. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, R^3, R^5, R^7, Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

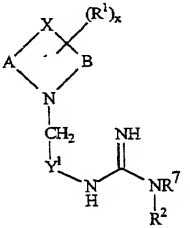


with a compound of the formula

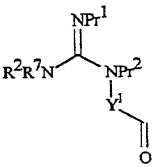


wherein Q^1, R^{2A}, R^{3A}, and R^{7A} are any of the groups defined for Q, R^2, R^3, and R^7, respectively, or protecting groups.

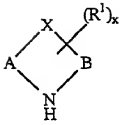
21. A method of making a compound of the formula



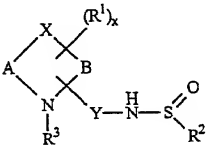
wherein A, B, x, R^1, R^2, and X are as recited in claim 1 and Y^1 is a C_1 to C_9 alkylene group, said method comprising the step of reacting a compound of the formula



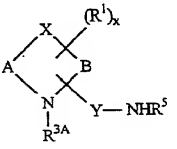
(wherein Pr^1 and Pr^2 are protecting groups) with a compound of the formula



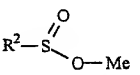
22. A method of making a compound of the formula



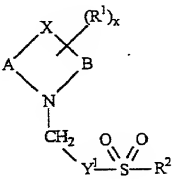
wherein A, B, x, R^1, R^2, R^3, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula



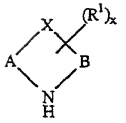
(wherein R^{3A} is C_1 to C_7 hydrocarbyl or a protecting group) with a compound of the formula



23. A method of making a compound of the formula

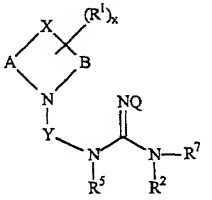


wherein A, B, x, R^1, R^2, and X are as recited in claim 1 and Y^1 is a C_1 to C_9 alkylene group, said method comprising the step of reacting a compound of the formula

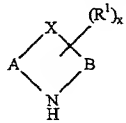


with a compound of the formula R^2-SO_2-Y^1-CHO.

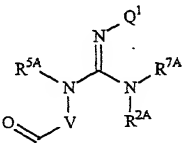
24. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, R^5, R^7, Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

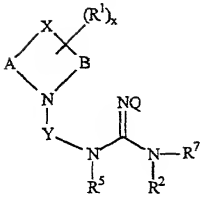


with a compound of the formula

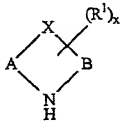


wherein V is C_1 to C_9 alkylene, and Q^1, R^{2A}, R^{5A} and R^{7A} are any of the groups defined for Q, R^2, R^5 and R^7, respectively, or a protecting group.

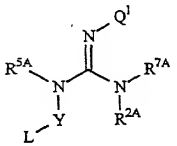
25. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, R^5, R^7, Q, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

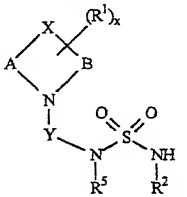


with a compound of the formula

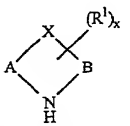


wherein L is a leaving group, and Q^1, R^{2A}, R^{5A} and R^{7A} are any of the groups defined for Q, R^2, R^5 and R^7, respectively, or a protecting group.

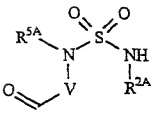
26. A method of making a compound of the formula



wherein A, B, x, R^1, R^2, R^5, X and Y are as recited in claim 1, said method comprising the step of reacting a compound of the formula

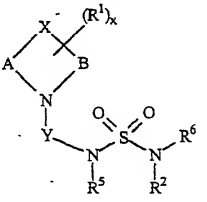


with a compound of the formula

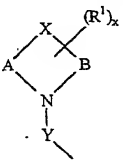


wherein V is C_1 to C_9 alkylene, and R^{2A} and R^{5A} are any of the groups recited for R^2 and R^5, respectively, or a protecting group.

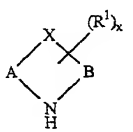
27. A method of making a compound of the formula



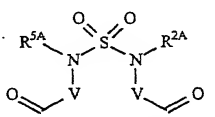
wherein A, B, x, R^1, R^2, R^5, X and Y are as recited in claim 1 (provided that the moiety



constitutes a group falling within the definition of R^6), said method comprising the step of reacting a compound of the formula

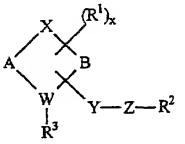


with a compound of the formula



wherein V is C_1 to C_9 alkylene, and R^{2A} and R^{5A} are any of the groups recited for R^2 and R^5, respectively, or a protecting group.

28. The use of an H_3 receptor ligand in the manufacture of a medicament for modifying H_3 receptor activity in a patient, said H_3 receptor ligand being a compound of the formula



wherein

A is $(CH_2)_m$, m being from 1 to 3;

B is $(CH_2)_n$, n being from 1 to 3;

x is from 0 to 2;

R^1 is C_1 to C_{10} hydrocarbyl, in which up to 2 carbon atoms may be replaced by O, S or N, and up to 2 hydrogen atoms may be replaced by halogen;

R^2 is H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O, S or N, and up to 3 hydrogen atoms may be replaced by halogen;

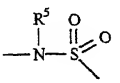
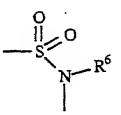
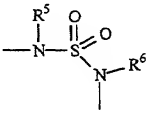
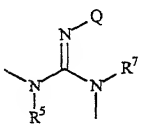
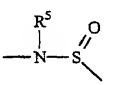
R^3 is absent when -Y-Z-R^2 is attached to W, or is H or C_1 to C_7 hydrocarbyl when -Y-Z-R^2 is not attached to W;

W is nitrogen;

X is $-CH_2-$, -O- or $-NR^4-$, R^4 being H or C_1 to C_3 alkyl;

Y replaces a hydrogen atom on any of A, B, W and X, and is C_2 to C_{10} alkylene, in which one non-terminal carbon atom may be replaced by O; and

Z is






or


wherein R^5, R^6 and R^7 are independently H or C_1 to C_{15} hydrocarbyl, in which up to 3 carbon atoms may be replaced by O or N, and up to 3 hydrogen atoms may be replaced by halogen, and Q is H or methyl, or Q is linked to R^5 or R^7 to form a five-membered ring or Q is linked to R^2 to form a six-membered ring,

or a pharmaceutically acceptable salt thereof.

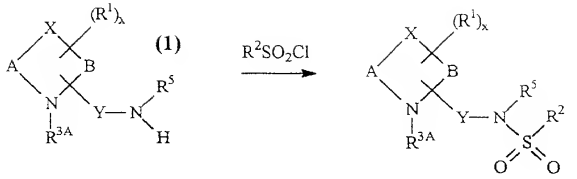


Figure 1

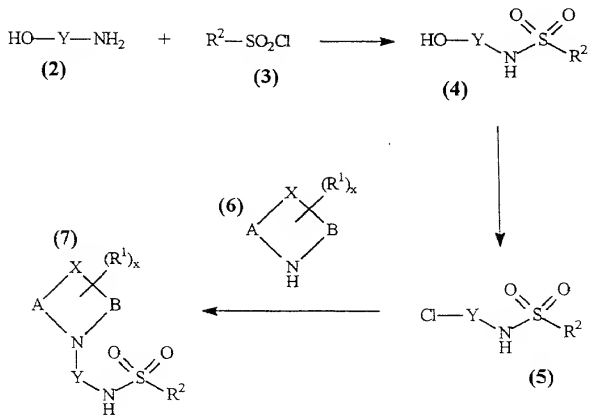


Figure 2

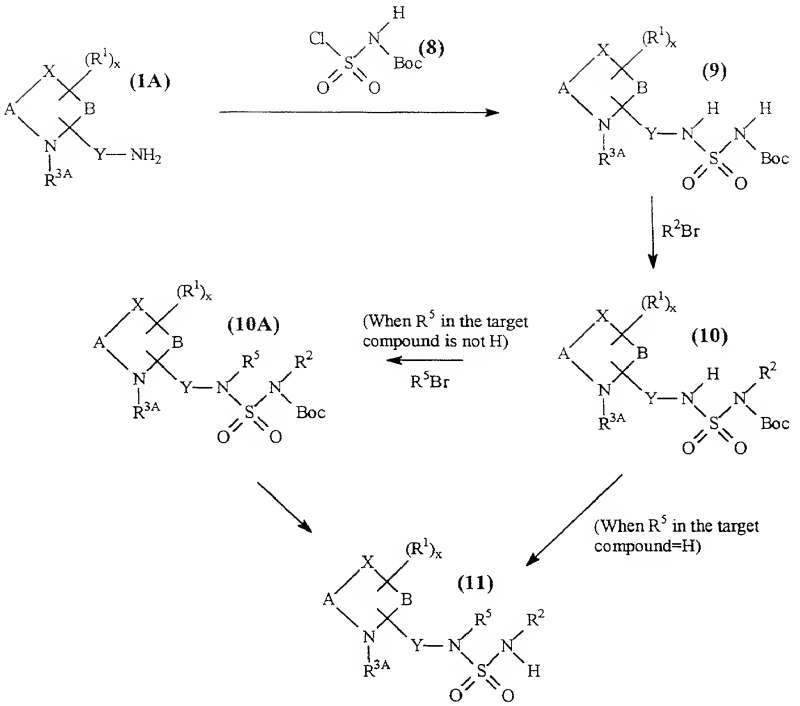

(1A)
(8)
(9)
R2Br
(10A)
(When R5 in the target compound is not H)
R5Br
(10)
(When R5 in the target compound=H)
(11)

Figure 3

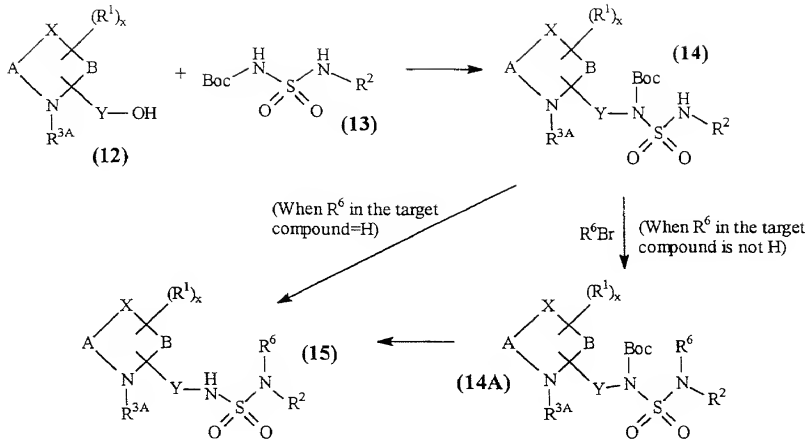

(12)
(13)
(14)
(When R6 in the target compound=H)
R6Br
(When R6 in the target compound is not H)
(14A)
(15)

Figure 4

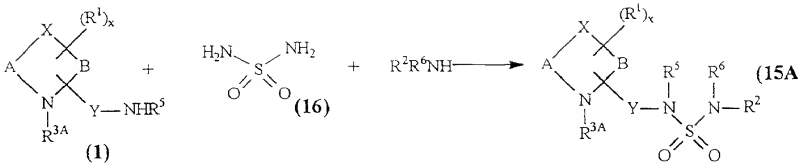


Figure 5

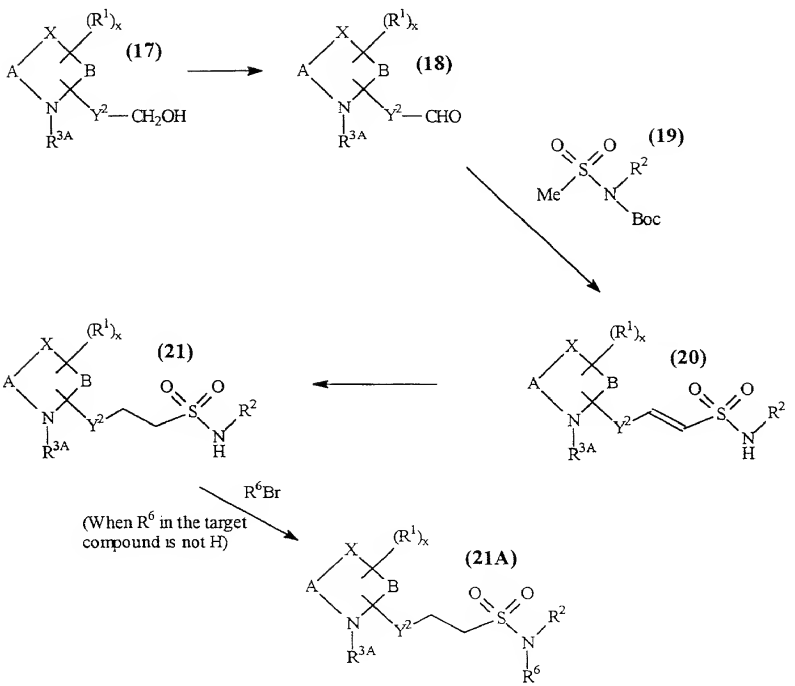


Figure 6

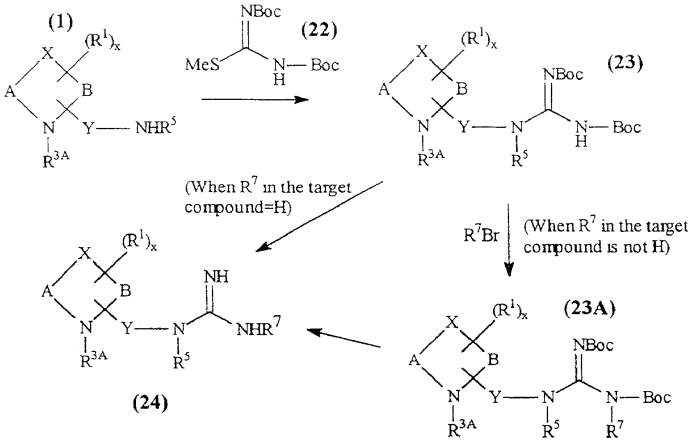


Figure 7

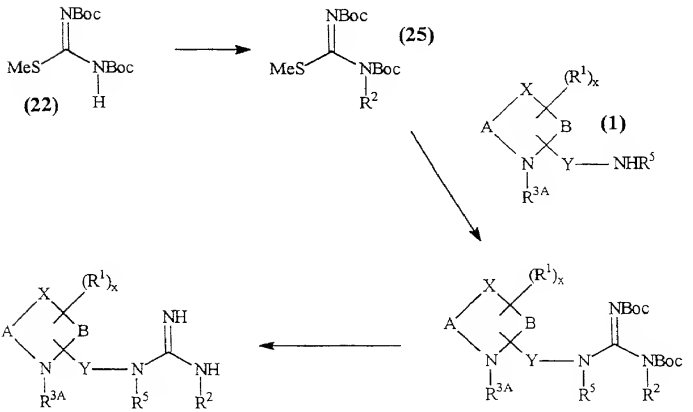


Figure 8

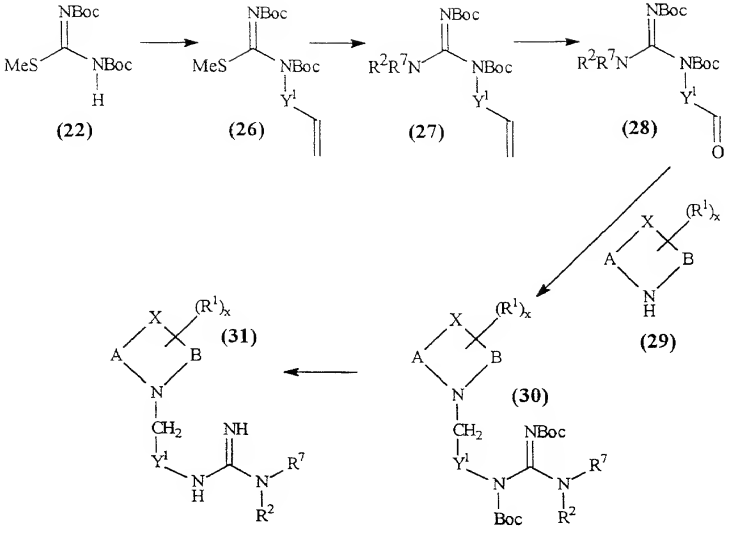


Figure 9

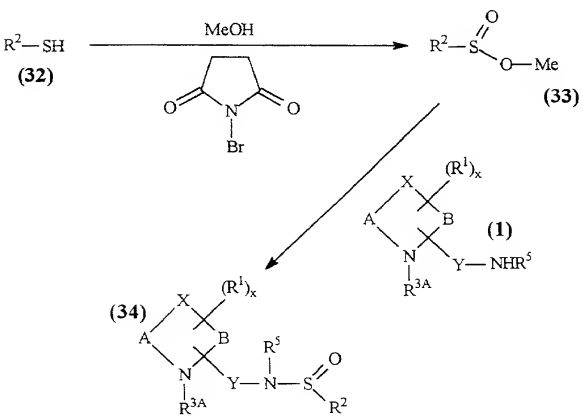


Figure 10

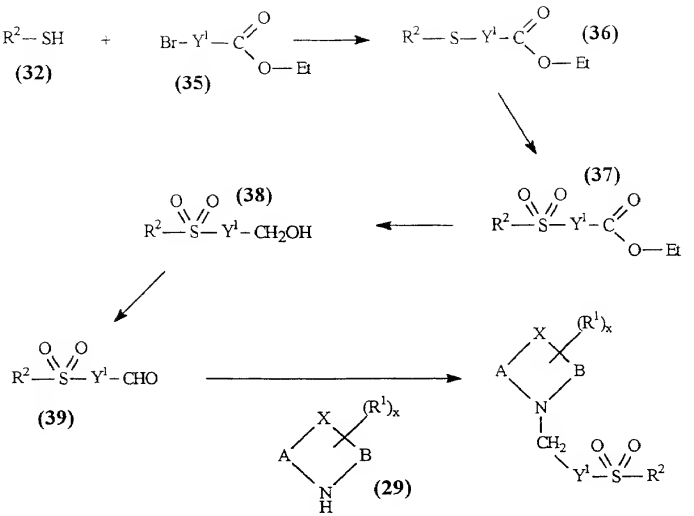

R2—SH
(32)
Br-Y1—C(=O)—O—Et
(35)
R2—S—Y1—C(=O)—O—Et
(36)
(37)
R2—S(=O)(=O)—Y1—C(=O)—O—Et
(38)
R2—S(=O)(=O)—Y1—CH2OH
R2—S(=O)(=O)—Y1—CHO
(39)
(R1)x
X
A
B
N
H
(29)
CH2
Y1—S(=O)(=O)—R2

Figure 11

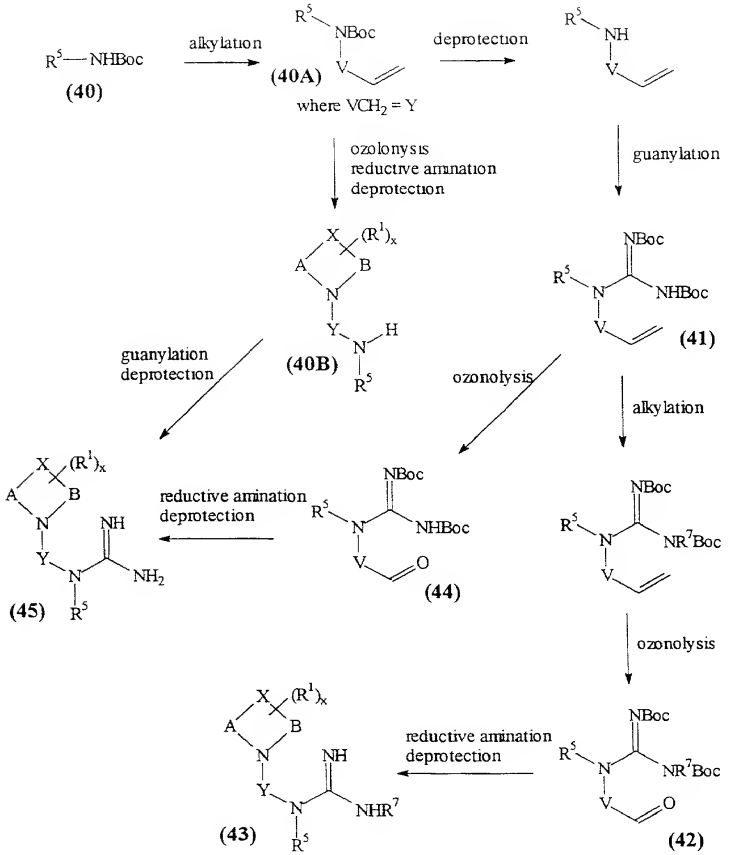

alkylation
deprotection
(40)
(40A)
where VCH2 = Y
ozolonysis
reductive amination
deprotection
guanylation
(40B)
(41)
guanylation
deprotection
ozonolysis
alkylation
reductive amination
deprotection
(44)
(45)
ozonolysis
reductive amination
deprotection
(43)
(42)

Figure 12

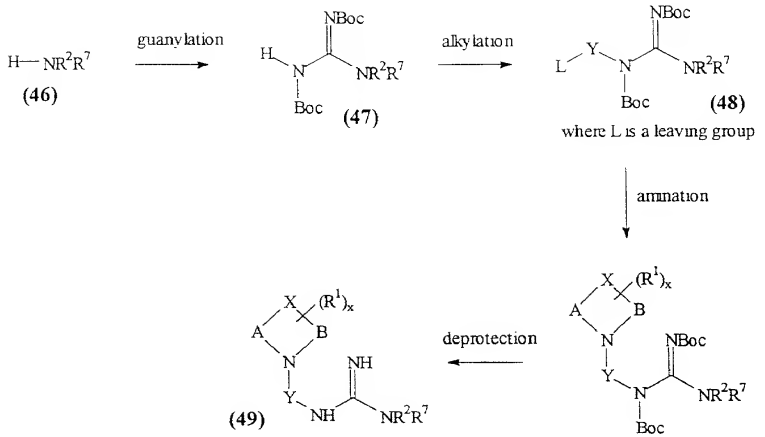


Figure 13

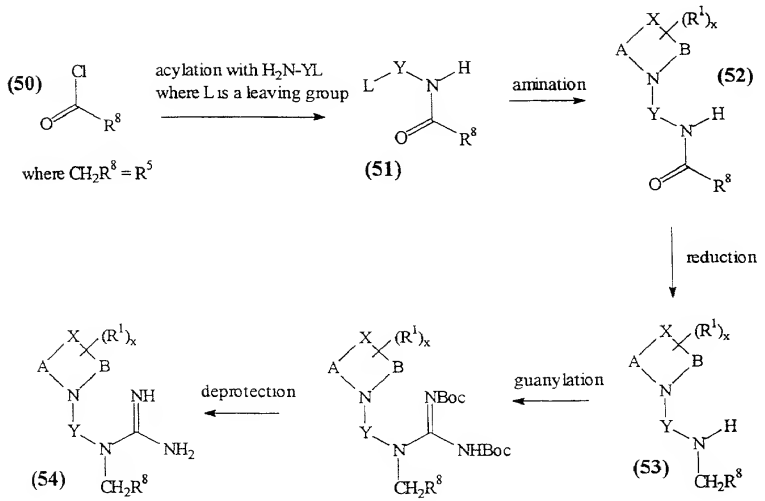


Figure 14

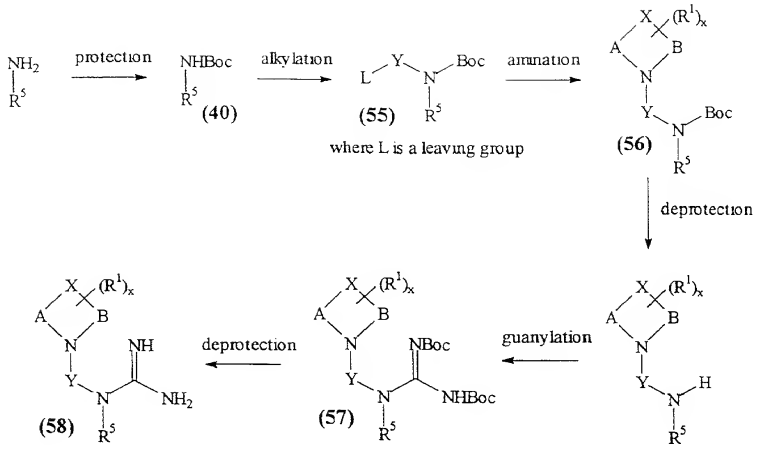


Figure 15

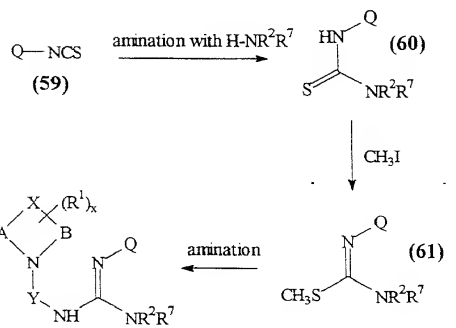


Figure 16

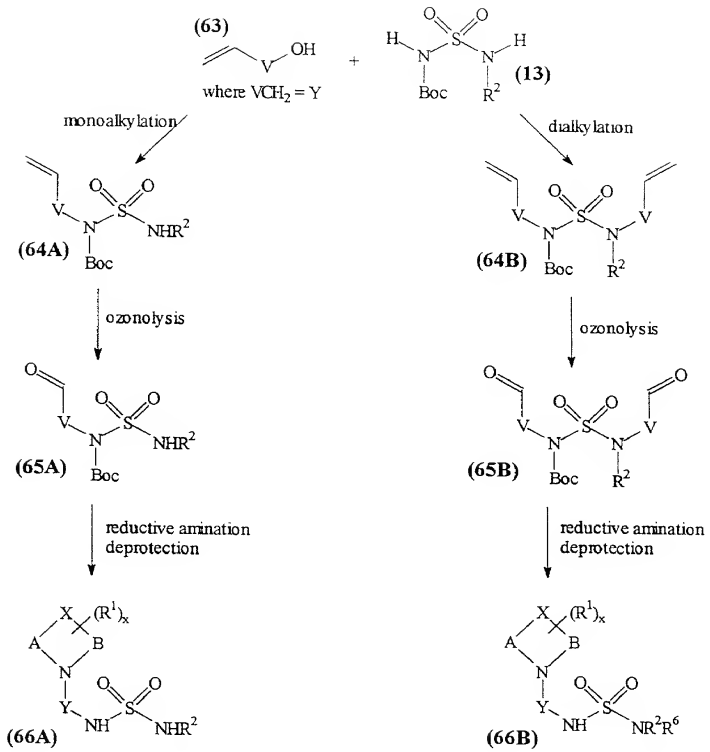

(63)
where VCH2 = Y
(13)
monoalkylation
dialkylation
(64A)
(64B)
ozonolysis
ozonolysis
(65A)
(65B)
reductive amination
deprotection
reductive amination
deprotection
(66A)
(66B)

Figure 17

Atty. Dkt. No. 040283/0183

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE.

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Histamine H_3 Receptor Ligands

(Attorney Docket No. 040283/0183)

the specification of which (check one)

___ is attached hereto.

_x_ was filed on February 15, 1999 as United States Application Number or PCT International Application Number PCT/GB99/00464 and was amended on _____ (if applicable).

THAT I do not know and do not believe that the same invention was ever known or used by others in the United States of America, or was patented or described in any printed publication in any country, before I (we) invented it;

THAT I do not know and do not believe that the same invention was patented or described in any printed publication in any country, or in public use or on sale in the United States of America, for more than one year prior to the filing date of this United States application;

THAT I do not know and do not believe that the same invention was first patented or made the subject of an inventor's certificate that issued in any country foreign to the United States of America before the filing date of this United States application if the foreign application was filed by me (us), or by my (our) legal representatives or assigns, more than twelve months (six months for design patents) prior to the filing date of this United States application;

THAT I have reviewed and understand the contents of the above-identified specification, including the claim(s), as amended by any amendment specifically referred to above;

THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56

Atty. Dkt. No. 040283/0183

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application Number	Country	Foreign Filing Date	Priority Claimed?	Certified Copy Attached?
9803536 3	Great Britain	February 19, 1998	Yes	No

I HEREBY CLAIM the benefit under Title 35, United States Code § 119(e) of any United States provisional application(s) listed below.

U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

I HEREBY APPOINT the following registered attorneys and agents of the law firm of FOLEY & LARDNER to have full power to prosecute this application and any continuations, divisions, reissues, and reexaminations thereof, to receive the patent, and to transact all business in the United States Patent and Trademark Office connected therewith:

STEPHEN A. BENT	Reg No	29,768
DAVID A. BLUMENTHAL	Reg No.	26,257
BETH A. BURROUS	Reg. No.	35,087
ALAN I. CANTOR	Reg. No	28,163
WILLIAM T. ELLIS	Reg No	26,874
JOHN J. FELDHAUS	Reg. No	28,822
PATRICIA D. GRANADOS	Reg. No.	33,683

Atty. Dkt No 040283/0183

JOHN P. ISACSON	Reg No	33,715
MICHAEL D. KAMINSKI	Reg No	32,904
LYLE K KIMMS	Reg No	34,079
KENNETH E. KROSIN	Reg. No.	25,735
JOHNNY A. KUMAR	Reg. No.	34,649
GLENN LAW	Reg. No.	34,371
PETER G. MACK	Reg. No.	28,001
BRIAN J MC NAMARA	Reg. No.	32,789
SYBIL MELOY	Reg No	22,749
RICHARD C PEET	Reg No	35,792
GEORGE E. QUILLIN	Reg. No.	32,792
COLIN G. SANDERCOCK	Reg. No.	31,298
BERNHARD D SAXE	Reg. No.	28,665
CHARLES F. SCHILL	Reg. No.	27,590
RICHARD L. SCHWAAB	Reg. No.	25,479
ARTHUR SCHWARTZ	Reg. No.	22,115
HAROLD C. WEGNER	Reg. No.	25,258

and I request that all correspondence be directed to:

Bernhard D. Saxe
~~FOLEY & LARDNER~~
Washington Harbour
3000 K Street, N.W., Suite 500
Washington, D.C. ~~20007-5109~~

Telephone: (202) 672-5427
Facsimile: (202) 672-5399

I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

Name of first inventor	Sarkis Barret KALINDJIAN
Residence	Banstead, Surrey, Great Britain GB
Citizenship	Great Britain
Post Office Address	46 Colcokes Road, Banstead, Surrey, Great Britain SM7 2EJ
Inventor's signature	
Date	31/9/00

Atty Dkt. No. 040283/0183

Name of second inventor	Ildiko Maria BUCK
Residence	London, Great Britain
Citizenship	Great Britain GB3
Post Office Address	60 Hermitage Road, London, Great Britain N4 1LY
Inventor's signature	
Date	28/9/00

Name of third inventor	Ian Duncan LINNEY
Residence	Guildford, Surrey, Great Britain GB3
Citizenship	Great Britain
Post Office Address	6 Monro Drive, Guildford, Surrey, Great Britain GU2 6PS
Inventor's signature	
Date	28/9/00

Name of fourth inventor	Gillian ~~Farfull~~ WATT
Residence	West Croydon, Surrey, Great Britain
Citizenship	Great Britain GB3
Post Office Address	7 MayoRoad, , West Croydon, Surrey, Great Britain CR20 2QP
Inventor's signature	
Date	28-9-00

Name of fifth inventor	Elaine ~~Anne~~ ~~HARPER~~
Residence	Marston Morteyne, Beds, Great Britain
Citizenship	Great Britain GB3
Post Office Address	12 Parrish Close, Marston Morteyne, Beds, Great Britain MK43 0AG
Inventor's signature	
Date	28/9/00

Name of sixth inventor	Nigel Paul SHANKLEY
Residence	~~Tonbridge,~~ Great Britain
Citizenship	Great Britain GB3
Post Office Address	Carpenters, Knotley Hall, Chiddingstone Causeway, Tonbridge, Great Britain TN11 8JH
Inventor's signature	
Date	

Atty. Dkt. No. 040283/0183

DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I HEREBY DECLARE:

THAT my residence, post office address, and citizenship are as stated below next to my name;

THAT I believe I am the original, first, and sole inventor (if only one inventor is named below) or an original, first, and joint inventor (if plural inventors are named below or in an attached Declaration) of the subject matter which is claimed and for which a patent is sought on the invention entitled

Histamine H_3 Receptor Ligands

(Attorney Docket No. 040283/0183)

the specification of which (check one)

___ is attached hereto.

x was filed on February 15, 1999 as United States Application Number or PCT International Application Number PCT/GB99/00464 and was amended on ______ (if applicable).

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THAT I believe that the above-identified specification contains a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention, and sets forth the best mode contemplated by me of carrying out the invention; and

THAT I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to me to be material to patentability as defined in Title 37, Code of Federal Regulations, §1.56.

I HEREBY CLAIM foreign priority benefits under Title 35, United States Code §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or §365(a) of any PCT international application which designated at least one country other than the United States of America, listed below and have also identified below any foreign application for patent or inventor's certificate or of any PCT international application having a filing date before that of the application on which priority is claimed.

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9803536.3	Great Britain	February 19, 1998	Yes	No

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U.S. Provisional Application Number	Filing Date

I HEREBY CLAIM the benefit under Title 35, United States Code, §120 of any United States application(s), or § 365(c) of any PCT international application designating the United States of America, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of Title 35, United States Code, § 112, I acknowledge the duty to disclose information which is material to patentability as defined in Title 37, Code of Federal Regulations, § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application.

U.S Parent Application Number	PCT Parent Application Number	Parent Filing Date	Parent Patent Number

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DAVID A. BLUMENTHAL	Reg. No. 26,257
BETH A. BURROUS	Reg. No. 35,087
ALAN I. CANTOR	Reg. No. 28,163
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I UNDERSTAND AND AGREE THAT the foregoing attorneys and agents appointed by me to prosecute this application do not personally represent me or my legal interests, but instead represent the interests of the legal owner(s) of the invention described in this application.

I FURTHER DECLARE THAT all statements made herein of my own knowledge are true, and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application or any patent issuing thereon.

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